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FAMILIAL ADENOMATOUS POLYPOSIS: SCREENING, SURGERY AND DESMOID TUMOURS

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ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Medicine of the University of Helsinki, for public examination in lecture room 1, Meilahti Hospital, on October 7th, 2016, at 12 noon.

Helsinki 2016

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ISBN 978-951-51-2411-1 (paperback)
ISBN 978-951-51-2412-8 (PDF)
http://ethesis.helsinki.fi
Unigrafia
Helsinki 2016

To my family

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ABSTRACT

Familial adenomatous polyposis: Screening, surgery and desmoid tumours

Background: Familial adenomatous polyposis (FAP) is an autosomal dominant inherited syndrome, which is characterized by the development of hundreds or thousands of polyps in the colon and rectum. The first representative of the family (proband) is usually found because he/she presents with the symptoms that usually arise from multiple polyps or from cancer in the large intestine. After this diagnosis family members of that proband are called for screening. The prevention of otherwise inevitable colorectal cancer by prophylactic surgery should preferably be performed in early adulthood. The main surgical options are colectomy with ileorectal anastomosis and proctocolectomy with an ileal pouch-anal anastomosis or ileostomy. The screening of FAP has been shown to be effective in terms of diminishing the number of deaths from colorectal cancer, but the reduction in overall mortality remains unclear. Patients with FAP also carry an elevated risk of desmoid tumours, which are histologically benign proliferations of myofibroblasts, but are often difficult to treat. Desmoid tumours of FAP patients may also act more aggressively than their sporadic counterparts.

Aims: The aims of this PhD study were to analyse the short-term and long-term outcomes of the two different surgical procedures: colectomy with ileorectal anastomosis (IRA) and proctocolectomy with ileal pouch-anal anastomosis (IPAA). Further analysis was done on the need and the results of secondary proctectomies after IRA. The authors aimed to determine, whether familial screening reduces the overall mortality. The causes of death among Finnish FAP patients were studied. The risk of FAP among desmoid tumour patients was also studied. The disease outcome of patients with FAP-related tumours was compared with that of sporadic desmoid tumours in the Finnish population.

Patients and methods: Patient files of all 421 Finnish FAP patients archived since the year 1963 were studied. There were a total of 228 patients who had undergone IRA or IPAA between years 1963-2012. During the same period, 39 secondary proctectomies were performed for IRA patients. All the Finnish FAP patients until April 30th 2015 were included in the study for which the effect of screening was evaluated. Patients with a diagnosis of sporadic desmoid tumours between years 2000-2012 in Helsinki University Hospital district were invited to the FAP screening. They were offered both endoscopic screening and gene mutation testing. All 221 desmoid tumour patients from the year 1980 were included into the comparison of treatment between FAP associated and sporadic desmoid tumour.

Results: There were no significant differences in short term complications between IRA and IPAA. In the long run, however, more patients in the IRA group ended up with ileostomy than in the IPAA group. The total cumulative survival was better

after IPAA than IRA, but if the analysis only took into account IRA performed after the IPAA era (from the year 1992 onwards) there were no significant difference between the groups. Secondary proctectomy was performed on 28% of IRA patients. The cumulative risk for secondary proctectomy at 30 years was 53%. The majority of operations were performed for cancer or suspicion of cancer. The risk of rectal cancer after IRA was 13% and the risk of rectal cancer death was 7%. The crude mortality ratio of probands was 34.9 per 1000 person years and 8.3 among call-ups. The relative survival of probands was significantly lower than for their call-up counterparts, and 20 year relative survival for the call-ups was as high as 94%. Over two-thirds of all deaths were FAP related. Among sporadic desmoid tumour patients the prevalence of FAP was 4.8%. FAP diagnosis of these patients was evident by endoscopy. No cases of AFAP, which could sometimes be detectable only by gene mutation testing, were found. There were more intra-abdominal desmoids in the FAP desmoid tumour group, and the desmoid tumours were bigger and more often multiple than those in the sporadic desmoid tumour group. Majority of sporadic desmoid tumour patients were women, whereas among the FAP-related desmoid tumour population the gender distribution was equal and the FAP related desmoid tumour patients were younger. The treatment of FAP-related desmoids was more difficult, intralesional resections were more common and there are desmoid-related deaths (14% of all deaths) among FAP patients in contrast to sporadic desmoids.

Conclusions: Patients who underwent IPAA did not have more postoperative complications than patients with IRA. Substantial risk of rectal cancer remains after colectomy and IRA, so the IPAA procedure should be favored for the FAP patients with intermediate or severe polyposis. The risk of permanent stoma is also higher when proctectomy was performed in the second phase. The survival of probands is significantly lower than that of the general population whereas that of call-ups was comparable to the general population for up to 20 years after diagnosis. This is why the screening effort for the family members of the proband must be done. Desmoid tumour patients carry an elevated risk of FAP and therefore screening is usually indicated. Only asymptomatic patients with desmoid tumours situated in the extra truncal region may not need to be routinely screened. Desmoid tumours among FAP patients carry a more complex course of disease compared to patients with a sporadic desmoids, and thus the treatment of FAP-related desmoids is also more complex. If R0 resection is not achieved, the wait-and-see strategy might be a better choice than resection with involved margins.

TIIVISTELMÄ

Familiaalinen adenomatoottinen polypoosi:
Seulonta, kirurgia ja desmoidikasvaimet.

Tausta: Familiaalinen adenomatoottinen polypoosi (FAP) on suvuittain esiintyvä, autosomaalisesti vallitsevasti periytyvä oireyhtymä. Sille on ominaista satojen tai tuhansien polyyppien esiintyminen paksusuolen alueella. Suvun ensimmäinen jäsen havaitaan yleensä polyyppien tai jo kehittyneen syövän aiheuttamien oireiden perusteella. Heidän lähisukulaisensa kutsutaan seulontatutkimuksiin ennen oireiden alkua. Ilman hoitoa paksusuolen syöpä on lähes väistämätön, ja siksi kaikille familiaalista adenomatoottista polypoosia sairastaville suositellaan ennaltaehkäisevää kirurgiaa nuorella aikuisiällä. Yleisimmät leikkausvaihtoehdot ovat kolektomia ja ileorektaalinen liitos (IRA) tai proktokolektomia ja ileoanaalinen liitos (IPAA) ohutsuolen loppuosasta tehtävän säiliön avulla. Seulonnan on todettu vähentävän paksusuolensyöpäkuolleisuutta, mutta vaikutus kokonaiskuolleisuuteen on epäselvä. Familiaalista adenomatoottista polypoosia sairastavilla on kohonnut riski desmoidikasvaimiin. Desmoidikasvaimet ovat histologisesti hyvänlaatuisia, mutta toisinaan hankalahoitoisia. FAP potilaiden desmoidikasvaimet saattavat olla aggressiivisempia kuin desmoidikasvaimet, jotka esiintyvät erillään FAP:sta.

Tavoitteet: Tämän väitöskirjatutkielman tavoitteena oli arvioida eri leikkausmenetelmien (kolektomia ja ileorektaalinen liitos, ja proktokolektomia ja ileoanaalinen liitos) lyhyt- ja pitkäaikaistuloksia. Arvioimme kolektomiaryhmän potilaiden riskiä ajautua myöhemmin peräsuolen poistoon, ja myöhemmin tehtävän peräsuolen poiston tuloksia. Tavoitteenamme oli selvittää, vaikuttaako seulonta kokonaiskuolleisuuteen. Lisäksi selvitimme suomalaisten FAP-potilaiden kuolinsyyt. Desmoidikasvainpotilaiden riskiä sairastua FAP:iin tutkittiin. Sporadisesti esiintyvien ja FAP:iin liittyvien desmoidikasvaimien taudinkulkua verrattiin.

Potilaat ja menetelmät: Kaikki tunnetut suomalaiset 421 FAP-potilasta otettiin mukaan tutkimukseen vuodesta 1963 alkaen. Yhteensä 228 paksusuolen poistoa ja ileorektaalista tai ileoanaalista liitosta oli tehty 1963–2012. Samana aikana 39 myöhempää peräsuolen poistoa tehtiin ileorektaalisen ryhmän potilaille. Kaikki tunnetut FAP-potilaat otettiin tutkimukseen jossa selvitettiin seulonnan vaikutusta eloonjäämiseen. Potilaat, joilla oli todettu desmoidikasvain vuosien 2000–2012 välillä, kutsuttiin FAP seulontaan. Heille tarjottiin sekä tähystys että geenitesti, mikäli näitä ei ollut aiemmin tehty. Kaikki 221 desmoidikasvaimeen vuoden 1980 jälkeen sairastunutta potilasta otettiin mukaan tutkimukseen, jossa FAP:iin liittyvien ja sporadisten desmoidikasvaimien hoitoa verrattiin.

Tulokset: Lyhyen aikavälin komplikaatioissa ei ollut IRA- ja IPAA-ryhmien välillä eroa. IRA-ryhmässä useampi potilas päätyi pysyvään avanteeseen. IPAA-ryhmässä oli kokonaisuudessaan parempi eloonjäämisen ennuste, mutta mikäli otettiin

huomioon vain IPAA-aikakaudella tehdyt leikkaukset (vuodesta 1992 alkaen), merkittävää eroa ei havaittu. Myöhempi peräsuolen poisto tehtiin 28%:lle IRA potilaista. Kumulatiivinen riski myöhempään peräsuolen poistoon oli 53% 30 vuoden aikana. Suurin osa myöhemmistä peräsuolen poistoista tehtiin syövän tai syöpäepäilyn vuoksi. Peräsuolisyövän riski IRA:n jälkeen oli 13% ja peräsuolisyöpäkuoleman riski 7%. Oireiden perusteella todettujen potilaiden kuolleisuus oli 34,9 tuhatta asukasta kohden ja seulonnasta löytyneiden vastaava luku oli 8,3. Eloonjäämisen ennuste oli oireiden perusteella diagnosoiduilla merkittävästi matalampi kuin seulontaan osallistuneilla, joilla 20-vuotisennuste oli jopa 94% verrattuna normaaliväestöön. Yli kaksi kolmasosaa kuolemista oli FAPiin liittyviä. Sporadisten desmoidikasvainpotilaiden riski familiaaliseen adenomatoottisen polypoosiin oli 4,8%. Kaikilla heillä oli selvä suolen tähystyksessä havaittava polypoosi. Lieviä vain geenimutaatiotestillä havaittavia AFAP tapauksia ei löytynyt. FAPiin liittyvät desmoidikasvaimet olivat suurempia. Ne sijaitsivat useammin vatsaontelon sisällä ja niitä on useammin useita. Sporadiset desmoidikasvainpotilaat olivat useammin naisia, kun taas FAPiin liittyvien desmoidikasvainpotilaiden keskuudessa sukupuolijakauma oli tasainen, ja potilaat olivat nuorempia. FAPiin liittyvien desmoidikasvainten hoito oli hankalampaa. Kasvaimen koko poisto oli usein mahdotonta, ja desmoidikasvaimeen liittyviä kuolemia oli FAPiin liittyvien desmoidien ryhmässä 14%.

Päätelmät: IPAA ryhmässä ei ollut komplikaatioita enempää kuin IRA ryhmässä. Peräsuolisyövän riski säilyy kolektomian ja ileorektaaliliitoksen jälkeen, jonka vuoksi proktokolekomia ja IPAA on ensisijainen vaihtoehto potilailla, joilla on kohtalainen tai runsas polypoosi. Lisäksi pysyvän avanteen riski on suurempi, jos peräsuolen poisto tehdään myöhemmässä vaiheessa. Oireiden perusteella diagnosoitujen potilaiden elinajanennuste on merkittävästi huonompi kuin normaaliväestön. Tämän vuoksi kaikki FAP-potilaiden lähisukulaiset pitäisi saada seulonnan piiriin. Desmoidikasvainpotilaiden riski sairastua FAP:iin on kohonnut, ja siksi seulonta on suositeltavaa tälle potilasryhmälle. Ainoa poikkeus saattaa olla suoliston suhteen oireettomat potilaat, joilla desmoidikasvain sijaitsee vartalon ulkopuolisella alueella. FAP:iin liittyvien desmoidikasvainpotilaiden taudinkulku on monimutkaisempi, ja tämän vuoksi myös hoito on usein monimutkaisempaa. Mikäli mikroskooppisesti täydelliseen kasvaimen poistoon ei päästä, saattaa aktiivinen seuranta olla parempi vaihtoehto kuin kasvaimen epätäydellinen poisto.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following papers, which are hereafter referred to in the text by the Roman numerals I – V.

I. Koskenvuo L, Mustonen H, Renkonen-Sinisalo L, Järvinen HJ, Lepistö A. Comparison of proctocolectomy and ileal pouch-anal anastomosis to colectomy and ileorectal anastomosis in familial adenomatous polyposis. *Fam Cancer*. 14:221-7, 2015.

II. Koskenvuo L, Renkonen-Sinisalo L, Järvinen HJ, Lepistö A. Risk of cancer and secondary proctectomy after colectomy and ileorectal anastomosis in familial adenomatous polyposis. *Int J Colorectal Dis*. 29:225-30, 2014.

III. Koskenvuo L, Pitkäniemi J, Rantanen M, Lepistö A. Impact of screening on survival in familial adenomatous polyposis. *J Clin Gastroenterol*. 50:40-44, 2016.

IV. Koskenvuo L, Peltomäki P, Renkonen-Sinisalo L, Gylling A, Nieminen TT, Ristimäki A, Lepistö A. Desmoid tumour patients carry an elevated risk of familial adenomatous polyposis. *J Surg Oncol*. 113:209-12,2016.

V. Koskenvuo L, Ristimäki A, Lepistö A. Comparison of sporadic and FAP associated desmoid tumours. Submitted.

ABBREVIATIONS

AFAP	Attenuated FAP
APC	Adenomatous polyposis coli protein
APC	Adenomatous polyposis coli gene
ASA	American Society of Anesthesiologists
C	Colectomy
CHRPE	Congenital hypertrophy of the retinal pigment epithelium
CI	Confidence interval
COX-2	Cyclooxygenase inhibitor 2
CRC	Colorectal cancer
ECM	Extracolonic manifestation
ESMO	European Society for Medical Oncology
FAP	Familial adenomatous polyposis
FGP	Fundic gland polyp
HNPCC	Hereditary nonpolyposis colorectal cancer, Lynch syndrome
IPAA	Ileal pouch-anal anastomosis
IQR	Interquartile range
IRA	Ileorectal anastomosis
MAP	MUTYH/MYH associated polyposis
MIM	Mendelian inheritance of man
MLPA	Multiplex ligation-dependent probe amplification
M(ut)YH	Mutation Y Homologue
NCCN	National Comprehensive Cancer Network
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PC	Proctocolectomy
SD	Standard deviation
SMR	Standardized mortality ratio
TME	Total mesorectal excision
WMD	Weighted mean difference

1. INTRODUCTION

Familial adenomatous polyposis (FAP) (MIM175000) is an inherited syndrome, which is characterized by the development of hundreds or thousands of adenomas in the colorectum (Bussey 1975). It is an autosomal dominant inherited disease. It refers to germline mutation of a gene called the adenomatous polyposis coli (*APC*). It is a rare syndrome with a frequency of about 1 per 10 000 inhabitants (Järvinen 1992, Bisgaard et al. 1994, Björk 1999). The progression of polyps starts in early adulthood (Vasen et al. 2008). There is a genotype-phenotype correlation with respect to the severity of colorectal polyposis. The patient has a virtually 100% risk of progression to colorectal cancer by the age of 35-40 years, if the condition is left untreated (Bussey 1975, Bisgaard et al. 1994).

The first patient of the family, who is referred to as the proband, presents clinical symptoms of FAP. The symptoms are usually due to profound colorectal polyposis or colorectal cancer (Bussey 1975, Bülow 1991). Other symptoms or findings may also reveal FAP. These are for example, desmoid tumours in any part of the body or fundic gland polyps (FGP) in gastroscopy (Bülow 1991). The family members of the proband are contacted to make an appointment (hereafter referred to as call-ups) for screening, which is hopefully before any symptoms arise. These call-ups that attend the first screening are on average 15-20 years younger than their symptomatic family members. Screening can be accomplished through endoscopy or by genetic testing.

The first goal of the surveillance is preparing the patient for optimally timed prophylactic surgery. The main treatment method involves the excision of the colon or colon and rectum. There are many controversial aspects concerning such prophylactic surgery. For cases in which malignant lesion has already been diagnosed, the decision is easy: surgery must be done as soon as possible. In many situations, however, this is not a case. There might be a young healthy patient with no clear suspicion of malignancy, who ends up to an extensive operation. Moreover, the extent of the operation has to be decided. The choice can be between the excision of the colon and subsequent continuation of the surveillance of the rectum and the excision of the entire colorectum along with the ileoanal anastomosis o ileostomy. If the rectum is left *in situ*, the risk of rectal cancer remains. The estimated cumulative risk of rectal cancer after 40 years is reported to be up to 32% (Bülow et al. 2000). At present, proctocolectomy with ileal pouch-anal anastomosis (IPAA) is

considered as the treatment of choice for a majority of patients, but there are also arguments in favour of colectomy and ileorectal anastomosis (IRA) (Vasen et al. 2008, Campos 2014).

The present effective prophylactic and cancer treatment of colorectal problems has led to a situation where other common premalignant or malignant conditions of FAP have come more important when evaluating the survival of FAP patients. Almost all FAP patients will eventually develop adenomas in the upper gastrointestinal tract and they also have a risk of progression into cancer (Bülow et al. 2004). Desmoid tumours are overexpressed among FAP patients. About 10-15% of FAP patients will have desmoid tumour during their lifetime (Nieuwenhuis et al. 2008, Campos et al. 2015). Desmoid tumours are not histologically malignant, but they may be as harmful as malignant tumours in the abdominal cavity. The treatment of widely growing desmoid tumours can be difficult and recurrences are commonplace. Nevertheless, desmoids are not malignant, and desmoid tumours are along with duodenal cancer the most common reason of deaths among FAP patients after the colorectal cancer (de Campos et al. 2010).

The preventive effect of screening on colorectal deaths has been well documented and reported, but still there remain questions of the effectiveness of systematic screening in reducing the overall mortality (Heiskanen et al. 2000, Bülow 2003, Gibbons et al. 2011). Moreover, the optimal surgical procedure for every individual patient by taking into consideration the patient's age, gender, and severity of polyposis and the location of the mutation as well as the patients' own wishes still remains under debate.

2. REVIEW OF THE LITERATURE

2.1 Hereditary colorectal cancer syndromes

There were about 3000 new colorectal cancer cases found in Finland in 2014. Colorectal cancer is the third most common cancer among men and the second most common cancer among women, and the incidence is rising. (Finnish cancer registry) About 30% of all colorectal cancer patients have a positive family history of colorectal cancer, which is indicative of a hereditary component. However, only 5% of colorectal cancer patients have a Mendelian inherited disorder with one specific gene mutation (Carballal et al. 2014, Brosens et al. 2015) (Table 1).

Table 1 *Hereditary colorectal cancer syndromes*

Syndrome	Gene mutation	Inheritance
Lynch/Lynch-Mecklin/HNPCC (MIM120435)	*MLH1, MSH2, MSH6, PMS2* or *EpCAM*	Autosomal dominant
Familial colorectal cancer type X	Not known	Not known
FAP (also attenuated) (MIM175000)	*APC*	Autosomal dominant
MUTYH-associated polyposis (MIM604933)	*MUTYH*	Autosomal recessive
Peutz-Jeghers syndrome (MIM175200)	*STK11*	Autosomal dominant
Juvenile polyposis syndrome (MIM174900)	*SMAD4, BMPR1A*	Autosomal dominant
Hereditary mixed polyposis syndrome (MIM601228)	*GREM1*	Autosomal dominant
Serrated polyposis syndrome	Not known	Not known

(Carballal et al. 2014, Brosens et al. 2015, OMIM database)

The most common of the known Mendelian disorders is Lynch syndrome (Lynch et al. 2003). The lifetime risk for colorectal cancer ranges between 10% and 74% (Brosens et al. 2015). Cancers are predominantly situated in the proximal colon and arise through the adenoma-carcinoma sequence; the sequence is much faster than among the sporadic cases. There are normally not many adenomas found in colonoscopy in contrast to the polyposis syndromes. Cancer is usually diagnosed about 10 years before sporadic cases (Giardiello et al. 2014). Lynch syndrome related colorectal cancers have an

improved survival among patients compared to those who have sporadic cancers at the same stage. Lynch syndrome is associated with several extracolonic cancer risks. The most common are endometrial cancer in women and urinary tract cancers. (Lynch et al. 2003, Brosens et al. 2015)

There are families for which the criteria for Lynch syndrome are fulfilled, except that the mutation in genes involved is not found. This syndrome is called familial colorectal cancer type X. These patients tend to have colorectal cancer at older age and the colorectal cancers are less likely to be located in the right colon than the Lynch syndrome patients. Tumours are less likely to be mucinous and multiple. Otherwise the disease closely resembles that of the classic Lynch syndrome. (Valle et al. 2007)

FAP is the second most common colorectal cancer syndrome and it is described in detail in this dissertation. It is also an autosomal dominant inherited syndrome that manifests hundreds or even thousands of adenomatous polyps throughout the colon and the rectum. The colorectal cancer risk for FAP patients is almost 100%, if left untreated (Bussey 1975, Bisgaard et al. 1994). There are fewer polyps and the colorectal cancer risk is about 70% among attenuated FAP patients (Burt et al. 2004).

Human mutY homologue (MUTYH) -associated polyposis (MAP) is an autosomal recessive inherited syndrome. The phenotype is similar to that found in attenuated FAP (AFAP) patients, i.e. tens or hundreds of polyps are found throughout the colon and rectum. Polyposis is diagnosed later than in classical FAP. Polyps found among MAP patients can occur as adenomas or serrated polyps or both (Nielsen et al. 2011). The lifetime risk of colorectal cancer is around 80%. When CRC arises, the colectomy is indicated (Brosens et al. 2015).

The hamartomatous polyposis syndromes are very rare. The best known of these are Peutz-Jeghers syndrome and juvenile polyposis syndrome. Peutz-Jeghers syndrome is characterized by hamartomatous polyps throughout the gastrointestinal tract and typical mucocutaneous hyperpigmentation. In contrast, there are no skin findings among juvenile polyposis syndrome patients, only juvenile polyps found anywhere in the gastrointestinal tract. The risk of cancer at any site among Peutz-Jeghers syndrome can exceed 90%. The risk of colon cancer is reported to be about 40%. Juvenile polyposis patients carry about the same colorectal cancer risk. Annual or biannual colonoscopy is recommended for both syndromes. There are also some other hamartomatous polyposis syndromes such as *PTEN* hamartoma tumour syndrome. (Gammon et al. 2009)

The latest of polyposis syndromes to be described is hyperplastic polyposis syndrome (also known as serrated polyposis syndrome). The diagnostic criteria of the syndrome is at least five hyperplastic polyps occurring proximal to the sigmoid colon or one hyperplastic polyp occurring proximal to sigmoid colon with a at least one first-degree relative with hyperplastic polyposis or more than 30 hyperplastic polyps anywhere in the colon (Jass et al. 2000). Although traditionally considered as benign polyps, hyperplastic polyposis syndrome patients carry a relatively high risk of colorectal cancer, which can possibly exceed 50% (Hyman et al. 2004). A convincing germ line gene mutation responsible of this syndrome has not been found at the time of writing this dissertation.

2.2 History, epidemiology and registries of FAP

2.2.1 History

Timeline of FAP (Bülow et al. 2006)

1721: The first known description of **polyps of the colon**; Menzel reported a 15 year-old boy who died of dysentery and had colonic polyps in autopsy.

1881: Sklifasowski published the first known case report of **adenomatous polyposis**. He performed an operation where he removed large polyps through colostomy.

1924: The first known **proctocolectomy** was performed by Coffey and Lockhart-Mummery discovered the hereditary factors of FAP. He established **the first polyposis registry** in St. Mark's Hospital with Dr Cuthbert Dukes.

1933: Nissen performed the first known **proctocolectomy with straight ileoanal anastomosis** in Leipzig.

1939: Lochard-Mummery and Dukes reported the results of the **prophylactic sigmoidoscopies** performed on familial members of 10 families. They performed five **prophylactic colectomies** for them of which four succeeded.

1951: Gardner described a condition afterwards named as **Gardner's syndrome**. It included colorectal adenomas, desmoid tumours, bone tumours and soft cyst-like surface tumours.

1956: Lochard-Mummery and others reviewed **the surgical treatment recommendation for FAP**. They recommended a colectomy and ileorectal anastomosis because the proctocolectomy and ileoanal anastomosis gave no good functional results.

1975: **Bussey** published a thesis on the basis of the St. Mark's polyposis registry. It described familial adenomatous polyposis in detail.

1978: Park and colleagues introduced a new surgical procedure; **proctocolectomy with mucosectomy and ileal pouch-anal anastomosis.**

1986: Herrera and others described an association of FAP and deletion in **chromosome 5q**, and **Heald** described **stapled ileal pouch-anal anastomosis.**

1991: *APC* gene was characterised in detail in chromosome **5q21** (Groden et al. 1991, Joslyn et al. 1991, Kinzler et al. 1991, Nishisho et al. 1991).

2.2.2 Epidemiology/incidence

The incidence of FAP was 1.58 per million in Finland during years 1986-90 (Järvinen 1992). The incidence of FAP in the Danish population was 1.9 per million inhabitants (1990-99), whereas in the Swedish population during the years 1977-96 it was approximately 0.9 (Björk 1999, Bülow 2003). The prevalence in the Finnish population during the years 1986-90 was 26.3 per million inhabitants. The prevalence in the Swedish population was 31.6 (years 1992-96) per million inhabitants and in the Danish population it was 31.9 per million (Järvinen 1992, Björk 1999, Bülow 2003). Men and women are equally affected (Bussey 1975).

2.2.3 Registries

The polyposis registry of St Mark's hospital (London, UK) is the oldest registry. Dr Cuthbert Dukes and Mr J.P. Lockhart-Mummery founded the polyposis registry in 1924. The data of Finnish polyposis families have been collected since 1963 and enable continuing retrospective research from that date onwards. Professor Heikki Järvinen in Finland established the official research registry for polyposis patients in 1984. The Finnish registry was founded for the purposes of research, but many patients and families belonging to the research registry have also been beneficially treated and informed during research projects. Several registry patients have also avoided cancer because of having correctly timed prophylactic treatment. When comparing the colorectal cancer incidence and colorectal cancer deaths among FAP patients in Finland and elsewhere before and after starting the registry there has been a significant reduction in both (Järvinen 1992, Bülow 2003, Barrow et al. 2013).

The proband i.e. prospositus for polyposis refers to the first patient that presents usually with the symptoms due to colonic polyposis. Upon diagnosis of a proband, the calling-up of relatives for screening has become standard procedure (Bussey 1975). In registries these patients are separated into their own groups for the evaluation of the effectiveness of screening and prophylactic treatment.

2.3 Genetics of FAP

2.3.1 *APC* gene

The *APC* gene is identified as the gene responsible for familial adenomatous polyposis. Two different groups reported it independently; the group of Bert Vogelstein in Baltimore in collaboration with the group of Yusuke Nakamura

in Tokyo (Kinzler et al. 1991, Nishisho et al. 1991), and also by the group led by Ray White in Salt Lake City (Groden et al. 1991, Joslyn et al. 1991). The *APC* gene is situated in chromosome 5q21-q22. It is 139 kilobases in length and the longest coding transcript is 10.7 kilobases. The RefeSeq transcripts of *APC* gene contain variable number of exons (NM_000038: 16 exons, NM_001127510: 17 exons and NM_001127511: 14 exons). The longest transcript (NM_000038) of the gene encodes 2843 amino acids that form relatively large tumour suppressor protein called also APC. The APC protein contains binding sites for many other proteins including microtubules and the Wnt signaling pathway component called β-catenin (Goss et al. 2000, Aoki et al. 2007). A predominant tumour suppressor function of the APC protein is to control β-catenin levels in the cytoplasm (Kemler 1993). If the mutation occurs and the APC protein is truncated, the binding sites no longer exist and the overexpression of β-catenin will occur (Aoki et al. 2007).

According to the Knudson's two hit hypothesis (Figure 1) germline mutation in one copy of *APC* gene itself is insufficient for carcinogenesis to occur, but when the second copy mutates the development of colorectal cancer can start (Knudson 1971). In sporadic cancers a mutation in both copies must occur in every cell, but the *APC* gene mutation has been shown to be involved in sporadic colorectal cancer carcinogenesis, too (Powell et al. 1992). Mutation of the *APC* gene is the first step in the development of colorectal cancer via adenoma-carcinoma-sequence in FAP patients in addition to the sporadic colorectal cancer patients.

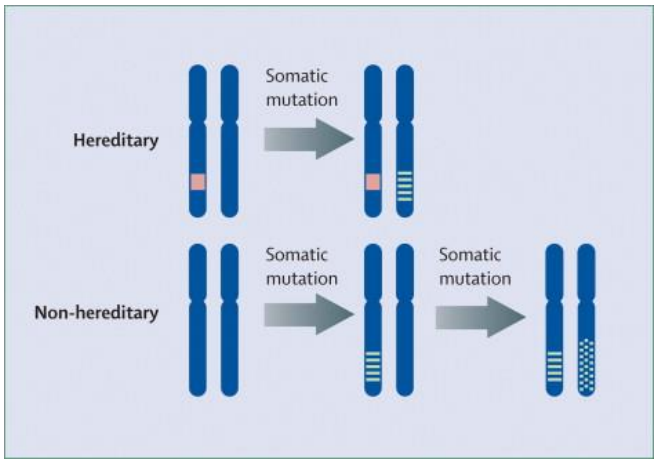


Figure 1 Knudson's two hit hypothesis of oncogenesis, adapted from Jozwiac J et al. 2008. Possible mechanisms of disease development in tuberous sclerosis, The Lancet Oncology 9:73-79, 2008 by permission from Elsevier Ltd.

More than 1600 germline mutations of *APC* have been reported (HGMD database). Of these 289 have reported to be pathogenic or likely pathogenic in ClinVar Database, which is known to contain relatively reliable variant classifications (clinvar database). Truncating mutations leads to a truncated protein due to premature termination of messenger RNA translation. Truncating mutations are the most common genetic defects in FAP. Truncations are either consequence from a nonsense mutation (direct stop codon, 32%), or small insertion or deletion (42%) leading to altered reading frame 'frameshift' with a premature stop codon in the downstream coding sequence. Moreover, splicing mutations are also frequent (8.3%) and some missense mutations have been described (Leoz et al. 2015, clinvar database). However, only three missense variants are uniformly classified as pathogenic or likely pathogenic in ClinVar as others have conflicting interpretations. Two out of these three missense variants (c.423G>T, p.(Arg141Ser), c.1548G>C, p.(Lys516Asn)) are located in the coding region next to consensus splice site and have confirmed to have effect on splicing.

The mutation site has a high impact on the phenotype expressed. If the mutation occurs in the middle of the *APC* gene, between codons 1250 and 1464, phenotype is usually more severe than a mutation in the border region of the gene (Nagase et al. 1992). The most frequent *APC* pathogenic mutation is located at codon 1309 (NM_000038.5: c.3924delA p.(Glu1309Lysfs*12), c.3925_3926delGA, p.(Glu1309Lysfs*5), c.3927_3931delAAAGA p.(Glu1309Aspfs), c.3925_3928delGAAA p.(Glu1309Argfs), c.3925G>T p.(Glu1309*)) (Leiden Open Variation database).

The *APC* germline mutations achieve almost 100% penetrance (Fearnhead et al 2001). Of the germline mutations the proportion of *de novo* mutations is reported to vary between 11-25% (Bisgaard et al. 1994, Björk et al. 1999).

2.3.2 Adenoma-carcinoma sequence in FAP

Genetics of colorectal cancer has been widely investigated. At least three different genetic pathways have been reported; adenoma-carcinoma sequence is the best studied. The *APC* gene mutation via the Wnt signaling pathway is responsible for the first step of this process (Figure 2). The mutation in the *APC* gene causes the formation of hundreds or thousands of primarily benign polyps. These polyps can undergo malignant progression, but this also requires a series of other mutations to happen in the polyp. There are many adenomas, however, and at least some will progress to cancer (Kinzler et al. 1996).

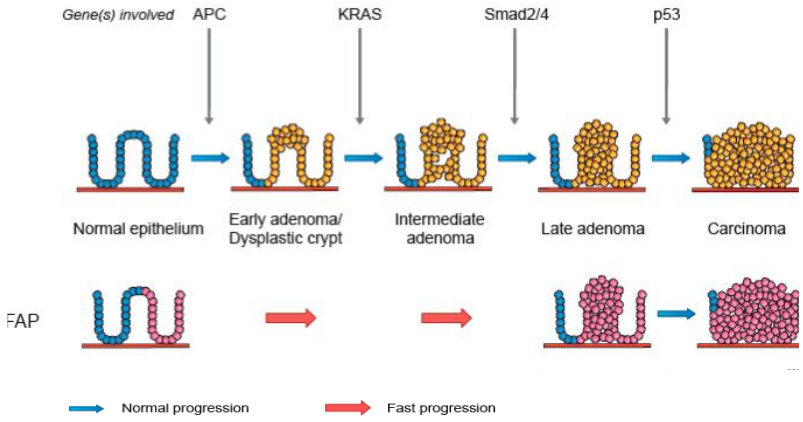


Figure 2 Adenoma carcinoma sequence, published with the permission obtained from the syscol website and adapted from Davies RJ, et al. Colorectal cancer screening: prospects for molecular stool analysis, Nature Review Cancer 5:199-209, 2005 by permission from Macmillan Publishers Ltd.

2.3.3 Genotype-phenotype correlation in polyposis

The mutation on different parts of the *APC* gene leads to different degrees of polyposis (Figure 3). A mutation between codons 1250 and 1464 leads to severe polyposis (>5000 colorectal polyps), and mutations in the 1309 codon are especially associated with severe polyposis with early onset of symptoms (Caspari et al. 1994). Mutations in attenuated polyposis has been reported to be situated in either the terminus of the *APC* gene, codons <157 or > 1595 or in the alternatively spliced site of exon 9 (codons 312-412) (Nieuwenhuis et al. 2007). Classical or intermediate polyposis is found among patients with mutations between codons 157 and 1595, excluding the areas of severe polyposis and attenuated polyposis in the middle of this region. In individuals of which the mutation is located between 976 and 1067 have reported to have a fourfold risk for duodenal adenomas (Bertario et al. 2003).

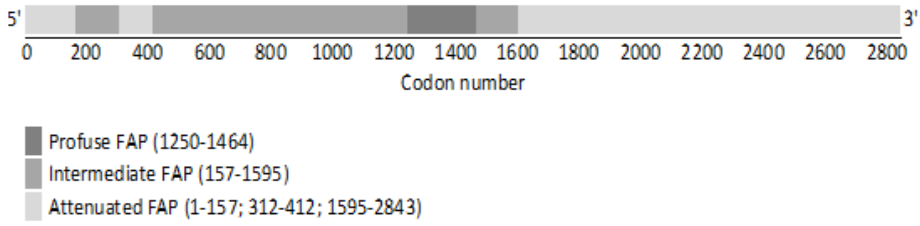


Figure 3 Severity of FAP according to codon in APC (nm 00038.5) (modified from Nieuwenhuis et al. 2011, Leoz et al. 2015)

2.3.4 Genotype-phenotype correlation in other manifestations

Desmoid disease has been linked to mutations near to the 3'-end of the gene, especially beyond codon 1444 (Bertario et al. 2001, Lefevre et al. 2008). Congenital hypertrophy of the retinal pigment epithelium is associated with codons between 311-1444 (Davies et al. 1995). Papillary thyroid carcinoma has been reported to be associated to mutations near to the 3'-end of the gene (Groen et al. 2008). Hepatoblastoma is associated for a quite wide range of mutations between 141 and 1751 codons (Hirschman et al. 2005, Groen et al. 2008). Osteomas are associated to mutations found in codons 767 to 1578 (Groen et al. 2008). Brain tumours, mostly those of medulloblastoma, are associated with mutations between codons 686–1217 (Attard et al. 2007). The genotype-phenotype correlation of extra-intestinal manifestations is illustrated in figure below (Figure 4).

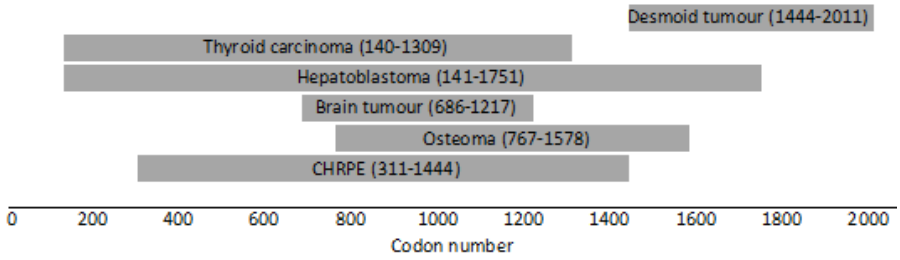


Figure 4 Extra intestinal manifestations according to affected codon in APC (nm 00038.5) (modified from Groen et al. 2008, Leoz et al. 2015).

2.4 Classification and histology of FAP

2.4.1 FAP

Classical FAP is defined as having over 100 adenomas presenting throughout the colorectum. The total number of polyps has been reported to vary from about 100 to 5000, the average is around 1000, and the density of polyps from 0.15 to 3 per square cm (Bussey 1975). Adenomas usually appear in adolescence. The patient's mean age at colonic polyp occurrence is 15.9 years (Petersen et al. 1991).

2.4.2 AFAP

A subset of polyposis patients expresses a milder phenotype than the classical FAP. This phenotype is termed attenuated familial adenomatous polyposis (AFAP). Typically the AFAP patient has fewer than 100 polyps in

the colorectal region, which are distributed dominantly on the right side of the colon. Rectal sparing of adenomas has also been reported (Lynch et al. 1995). Patients with this subtype have a delay in the onset of adenomatosis and a delay in the onset of colorectal cancer too (Knudsen et al. 2003). Mutations are situated at the either 3'- or 5'- end of the *APC* gene or in exon 9 (Soravia et al. 1998). The upper gastrointestinal manifestations such as FGPs and duodenal adenomas are usually found in AFAP as they are in classic FAP. In general, AFAP has been reported to be associated with a lower desmoid tumour risk. However, disease associating variants locating in specific region at the 3'-end of the *APC* gene associate to higher risk for desmoid tumours (Bertario et al. 2001).

2.4.3 Histology of FAP polyps

The polyps found in FAP are adenomatous polyps. They are pre-neoplastic polyps that consist of an overgrowth of hyperplastic intestinal mucus secreting epithelium (Bussey 1975). There are microscopic adenomas in FAP patients and these include single dysplastic crypts in normal looking mucosa around the polyps. The single dysplastic crypts, also called unicryptal adenomas, are pathognomonic for FAP (Novelli 2015). Polyps can be tubular adenomas, villous adenomas or intermediate tubulo-villous adenomas. Most of the polyps are under 0.5 cm in diameter and spread as a mat throughout the colon. The greater the diameter, the bigger is the risk of malignant histology. The histopathology of adenomas and adenocarcinomas in FAP are the same as the corresponding sporadic counterparts (Bussey 1975).

2.5 Screening and diagnostics of FAP

2.5.1 Clinical presentation

Patients with FAP nowadays present mostly without symptoms. Many patients are found because of a screening protocol or through the investigation of some other unrelated complaint. Some patients are referred for testing because of extracolonic manifestations such as supernumerary teeth, osteomas, desmoid tumour or congenital hypertrophy of the retinal pigment epithelium. If symptoms of polyposis are actually present, they may include bleeding, change in bowel habits, and abdominal pain (Yeo et al. 2013). The penetrance rate of the colonic polyposis disease for inherited cases is estimated to be close to 100% by the age of 40 years (Bisgaard et al. 1994). Over 70% of adenomas in classical FAP occur on the left side of the colon (Björk 1999). Figure 5 presents some manifestations in images.

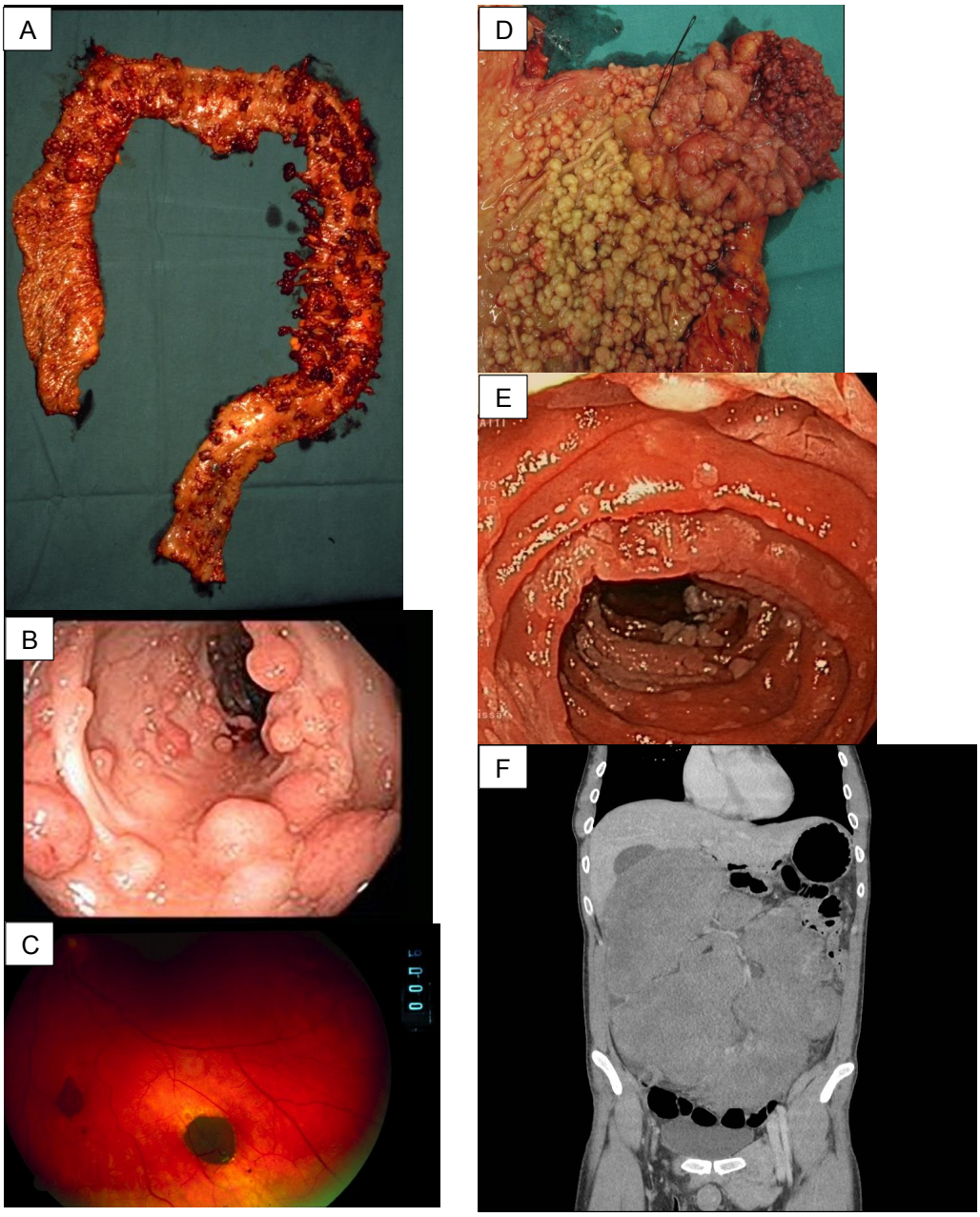


Figure 5 A) Opened proctocolectomy specimen of a patient with a severe polyposis, B) Endoscopic view from the colon of the FAP patient (picture creator: Miguel Rodrigues-Bigas, MD Anderson Cancer Center by permission from National Cancer Institute) C) CHRPE D) Opened gastrectomy specimen, gastric polyposis E) Endoscopy view, duodenal adenomatosis F) CT scan section of intra-abdominal desmoid tumour (pictures A, C-F from Heikki Järvinen and Anna Lepistö, Helsinki University Hospital, Finland).

2.5.2 Endoscopy

A person with 10 or more adenomas in the colorectum should raise suspicion of FAP. Classical FAP can be easily diagnosed by sigmoidoscopy in early adulthood. Biannual endoscopic screening of children at risk should begin as teenagers or at any age in the presence of FAP-related symptoms (Barnard 2009). The finding is usually obvious with hundreds or even thousands of polyps throughout the distal colon. In cases of milder phenotype, the diagnosis with sigmoidoscopy alone in not always clear. Total colonoscopy is recommended when there is a suspicion of AFAP as the polyps are often located on the right site of colon (Nielsen et al. 2007). After the diagnosis has been made, the annual screening for high risk adenomas should be continued until prophylactic surgery has taken place. Under colonoscopy the size of the biggest polyps should be recorded and the approximate polyp count and their distribution around colorectal area should also registered and several biopsies should be taken. The histology of the adenomatous polyps do not differ from that of the sporadic adenomas (Syngal et al. 2015).

The first upper endoscopy should be performed at the age of 30 at the latest or earlier if patients have upper GI symptoms. Duodenal cancer before age 30 is extremely rare (Brosens et al. 2005). The interval between the upper endoscopy is determined according to Spigelman stage (Vasen et al. 1997).

2.5.3 Genetic counseling and mutation testing

The patient must receive genetic counseling along with the mutation testing. The pretesting counseling session should include a review of patients' medical history, an evaluation of whether the genetic testing is appropriate, collecting the pedigree data, education of the patient and family about the medical aspects of potential disease, the patterns of inheritance, and the recommended screening and follow up guidelines. After a comprehensive and detailed first counseling has been carried out, the informed signed consent can be signed by the patient and blood draw for genetic testing can be taken. (Giardiello et al. 1997, Wong et al. 2001) If there is already a known mutation within a family, the genetic testing for that particular mutation can be performed. Some suggest that genetic screening should be performed between the ages of 10 to 12 years (Barnard 2009). Sporadic adenoma patients with over 10 adenomas in the colorectal area should be offered genetic testing. If a patient is the first individual in the family attending genetic testing, the full sequencing of the coding region of the *APC* gene is performed. Over 85% of all mutations can be found with classic sequencing. The other 10-15% of mutations are gross deletions and duplications, which can be detected with multiplex ligation-dependent probe amplification (MLPA) or other methods (Leoz et al. 2015). At present, the direct

sequencing is first done and if nothing is found, then screening is continued with MLPA. If the *APC* mutation is not found with MLPA either, and the clinical phenotype is similar to AFAP, then the MUTYH mutation screening should be done. Lately multigene panels have become available that allows detection of both sequence variants and deletions/duplications from the genes in one assay (Hedge et al. 2013). When the mutation is found all the information of the follow-up and treatment options are given. The patient is also advised to inform the family members about the risk of FAP. (Wong et al. 2001) First-degree relatives carry a 50% of risk of FAP. It remains the patient's responsibility to inform close family members. There are also a proportion of patients with undisputed FAP upon endoscopy, but no mutation can be found by gene mutation testing. The *APC* mutations were found in 80% of individuals with more than 1000 adenomas, 56% in those with 100–999 adenomas, 10% in those with 20-99 adenomas and 5% in those with 10-19 adenomas (Nielsen et al. 2007). Even though a known *APC* mutation cannot be found, and the patient fulfills the other diagnostic criteria for FAP based on the endoscopy findings, then regular surveillance and prophylactic surgery should still be undertaken. The colonoscopy screening should also be offered to first degree relatives.

2.6 Treatment of colonic polyposis

All patients with FAP are recommended to undergo prophylactic colonic or colorectal surgery because of the almost 100% risk of colorectal cancer. At present there are two different options: colectomy with ileorectal anastomosis (IRA) and proctocolectomy with ileal pouch-anal anastomosis (IPAA) (Figure 6). The traditional method of proctocolectomy and permanent Brooke's ileostomy is not widely used nowadays, because of the disadvantages related to permanent stoma formation. It is however sometimes used for patients with low rectal cancer, or sphincter dysfunction. In rare cases, Brooke's ileostomy is used when it becomes evident during the IPAA operation that the ileal pouch cannot be pulled down to the anus because of mesenteric desmoid or because of too short and fatty mesentery (Campos 2014). When the patient has severe co-morbidities, IPAA is not always performed, even if it were technically possible. In IRA procedure abdominal colectomy is performed with the anastomosis between the ileum and the rectum. The procedure of IPAA entails the colon and rectum being removed and the pouch is formed from the terminal ileum. The pouch is then attached to the anal canal after the mucosectomy of the anal stump. Parks and Nicholls introduced the proctocolectomy and hand-sewn anastomosis with the S-shaped pouch in 1978 (Parks et al. 1978) and two years later Utsunomiya described a simpler pouch in a J configuration (Utsunomiya et al. 1980). This hand-sewn anastomosis and J construction of the pouch is

still in use as a standard technique. Heald described an alternative technique with a stapled anastomosis between ileal pouch and the anus (Heald et al. 1986). A short segment of the rectal mucosa is left behind in the stapled technique. Diverting temporary ileostomy was originally routinely performed in connection with the IPAA and nowadays some centers also use it as a standard, and some other only when the patient has some complication risk-increasing factor such as immunodeficiency. (Weston-Petrides et al. 2008)

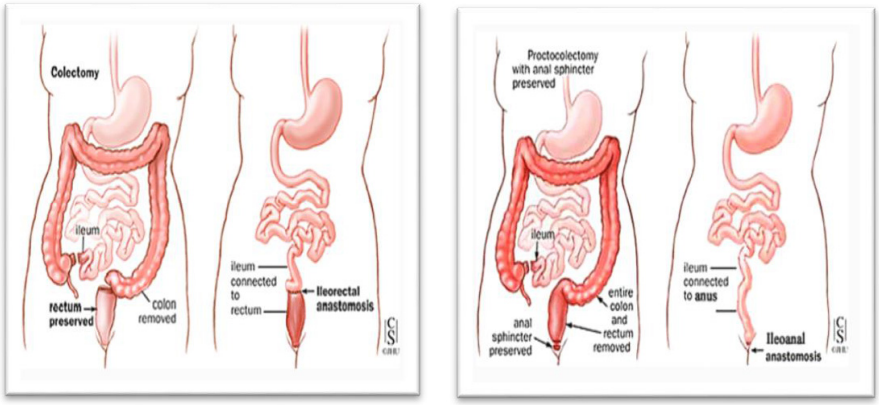


Figure 6 Illustration of colectomy and proctocolectomy procedures. Adapted from M'Koma AE, Wise, P.E., Muldoon, R.L. et al. Int J Colorectal Dis (2007) 22: 1143-63, 2007 by permission from Springer. by permission from Macmillan Publishers Ltd

When the patient does not have invasive cancer or severe dysplasia in preoperative biopsies and the operation is performed as a prophylaxis, the colonic dissection is usually performed close to the colonic wall. The rectal dissection should also be performed away from the presacral fascia (within the mesorectum) in order to avoid damage to the pelvic autonomic nerves. The total mesorectal excision (TME) technique is used, when the patient has a cancer or a premalignant lesion of the rectum (Kartheuser et al. 2006). The TME technique is also preferable for obese males with a narrow pelvis to help the pouch to fit down into the lower pelvis. Furthermore the colon is mobilized in an oncologically safe manner in the case of colon cancer.

In general, laparoscopic colorectal surgery has shown to be as safe as open colorectal surgery (Fichera et al. 2009, Jayne et al. 2010). There is also a trend among FAP patients towards laparoscopic approach. Comparing laparoscopic and open IPAA among FAP or ulcerative colitis patients there is no difference in mortality or morbidity between the groups (Polle et al. 2008). A possible reduction of post-operative desmoid formation related to

laparoscopic colectomies has also been shown (Vitellaro et al. 2014). Although that study had substantial limitations; the laparoscopic group was small and the follow-up time was significantly shorter for the laparoscopic than for the open groups (Vitellaro et al. 2014). Laparoscopic IPAA on the whole seems not be inferior to the open technique, but no major advantages for laparoscopic IPAA have been reported yet.

2.6.1 Timing of surgery

Timing of the prophylactic surgery is planned with due consideration with the patient's wishes, clinical characteristics of the polyposis and the location of mutation. Prophylactic surgery is usually performed between the ages 15 and 25. The risk of carcinoma before the age of 20 years is 1% for the whole FAP population (Vasen et al. 2008). However, those families that manifest a strong penetrance, malignant or premalignant lesions are not infrequently seen. There are several conditions when the postponement of surgery must be avoided. For patients having adenoma related symptoms, such as diarrhoea or bleeding, or those that have high-grade dysplasia or profuse adenomatosis or large adenomas, the surgery must not be postponed. The symptomatic polyposis is more likely to be severe and the risk of already existing carcinoma is also higher (Bülow 2003). If there is a verified or suspected cancer, surgery must be organized as soon as possible and in an oncologically safe manner. If the mutation site is in a high risk area for profuse polyposis (i.e. between codons 1250-1464) it is also an indication not to delay surgery (Campos 2014).

In the case of mild polyposis such as in AFAP at colonoscopy or on the basis of family history or genotype, the postponing of the surgery might be justified (Campos 2014). If the patient is asymptomatic, surgery can be postponed, but annual surveillance must be organized and the patient must be compliant with that surveillance (Campos 2014). It has also been proposed that a high-risk for desmoid tumour because of the mutation situation and/or family history could be a reason for postponing the surgery (Sturt et al. 2006).

2.6.2 Indications for IRA

When making the choice between IPAA and IRA, the patient's age, clinical condition and personal preferences must be taken account. Proctocolectomy followed by IPAA is nowadays the surgery of choice for classical FAP (Kartheuser et al. 1996). It restores gastrointestinal continuity and transanal defecation, and avoids a permanent stoma. Its major advantage is that the total proctocolectomy is accomplished in one session, and so the risk of

colorectal cancer is eliminated. There are still many unquestionable advantages in colectomy and IRA. Colectomy and IRA is easy to perform and it has relatively good functional results. Moreover, the secondary proctectomy and IPAA still remains an option after IRA for most patients. However, the risk of rectal cancer remains after IRA, and that risk is substantial (Iwama et al. 1994, Bülow et al. 2000, Aziz et al. 2006).

Colectomy and IRA is generally recommended for a patient with mild FAP as diagnosed by endoscopy or for AFAP by family history, endoscopy or mutation testing. If the rectum is reasonably clear of polyps, it can be left *in situ*. It has been suggested that there should be fewer than five polyps in the rectum, which are removable endoscopically. No adenomas with high grade dysplasia should be found in the rectum (Church et al. 2001). Further, the patient with the rectum left *in situ* should have good compliance for future annual rectal endoscopy, which is mandatory for all IRA operated FAP patients. Among young females the preservation of fecundity is important. It had previously been considered that fecundity after IPAA was reduced among FAP patients, but not after IRA (Olsen et al. 2003). However, a more recent study demonstrated there was no difference in fertility after IRA, IPAA, or proctocolectomy with ileostomy (Nieuwenhuis et al. 2010). The choice of operation type for patients with a high risk for desmoid disease due to family history or *APC* mutation site has recently been under debate. It has been suggested that after IRA a secondary proctectomy may be technically impossible because of the developing desmoid. Furthermore, if the proctectomy were actually possible, then the IPAA may still be prevented by a shortened and thickened mesentery because of an existing desmoid tumour (Vasen et al. 2008). Another study reported that the desmoid tumour prevented only one of 67 proctectomies, whereas 12% of the restorative proctectomies with ileal pouches did not succeed because of desmoid tumour (Church et al. 2014). No difference in desmoid formation after different procedures has been shown (Burgess et al. 2011).

2.6.3 Complications of surgery

The IPAA is a technically demanding procedure. It is associated with low mortality rates, but it is frequently accompanied by early and late complications. The IRA procedure also carries a risk of early and late complications even if it is technically easier to perform. The most frequent early complications include haemorrhage, surgical site infection, which can vary from mild wound infection to intra-abdominal septic condition such as leakage or abscess, and post-operative bowel obstruction. The overall complication rate after IRA has been reported to be around 20% and after IPAA around 27% (Madden et al. 1991, Ambroze et al. 1992, Tonelli et al.

1997, Duijvendijk et al. 1999, Soravia et al. 1999, Björk et al. 2001, Günther et al. 2003, von Roon et al. 2008, Campos et al. 2009, Bülow et al. 2013, Fazio et al. 2013). The complication prevalences from the different studies are presented in Table 2. A large meta-analysis that compared IPAA and IRA reported no significant difference in early post-operative complications between either procedure. However, increased 30 day reoperation rate was associated with IPAA; 23.4 vs. 11.6% (Aziz et al. 2006).

The prevalences of long-term adverse events and functional outcome are presented in Table 3. The rate of late complications after IPAA in general seems to be higher (Duijvendijk et al. 1999). The functional outcomes of IRA had better results in terms of reduced bowel movement, reduced need for night defecations, and reduced use of incontinence pads. There was more faecal urgency in the IRA group however. No difference was found between IRA and IPAA groups in the terms of bowel frequency at night, daytime incontinence, and need for antidiarrhoeal medication. (Aziz et al. 2006)

Overall short and long-term complication rates between primary and secondary IPAA have been reported to be at the same level (Penna et al. 1993, von Roon et al. 2008, Bülow et al. 2013). The overall IPAA failure rate reported ranged between 4% and 10% (Lepistö et al. 2002, Fazio et al. 2003, Lovegrove al. 2006, Hahnloser et al. 2007, von Roon et al. 2008, Bülow et al. 2013).

There is no difference observed in quality of life between IRA and IPAA operations, but in both groups the quality of life was inferior to the general population (van Duijvendijk et al. 2000, Aziz et al. 2006). When quality of life was compared in some other studies for FAP patients who underwent IPAA to normal population, there was no difference detected. There was however, a difference in the gastrointestinal quality of life in these studies. (Ganschow et al. 2010, Wolf et al. 2011)

Table 2 *Postoperative complication rates and reoperation rates in different studies comparing IRA and IPAA*

	Patients (No)				Complications (%)			Reoperations (%)	
Study*	Total	IPAA	Secondary IPAA	IRA	IPAA	Secondary IPAA	IRA	IPAA	IRA
Madden 1991	99	37		62	60%		21%	29%	6%
Ambroze 1992	105	94		21	26%		17%		
Tonelli 1997	38	24		14	21%		0%	13%	0%
Duijvendijk 1999	279	118		161				33%	17%
Soravia 1999	110	50		60	26%		23%	16%	13%
Björk 2001	102	20	39	43	25%	41%	28%		
Günther 2003	59	37		22	27%		14%		
von Roon 2008	185	107	78		24%	27%			
Campos 2009	69	27		42	33%		17%	5%	7%
Bülow 2013	84	59	25		10%	0%			
Fazio 2013	223	223			29%				
Average (Weighted)	**123**	**72**	**47**	**53**	**27%**	**26%**	**20%**	**24%**	**12%**

*Only the first authors' names have been given for full authorship see the reference section.

Table 3 *Need for reoperation within 30 days and the long-term outcomes (only statistically significant differences are shown)*

		No. of patients		Outcome (%)			Test for heterogeneity	
	No. of studies	IPAA	IRA	IPAA	IRA	OR or WMD*	χ^2	*P*
Need for reoperation within 30 days	6	274	362	23·4	11·6	2·11 (1·21, 3·70)	6·48	0·26
Long-term adverse events								
Perianal irritation	7	322	336	62·7	57·4	2·48 (1·36, 4·55)	9·63	0·09
Anastomotic stricture	5	198	300	8·1	2·0	3·84 (1·46, 10·11)	1·99	0·58
Carcinoma in pouch or rectum	5	187	271	0	5·5	0·13 (0·03, 0·61)	0·53	0·91
Abdominal reoperation on rectum pouch	6	290	289	3·1	27·7	0·10 (0·04, 0·23)	5·20	0·27
Functional outcome								
Bowel frequency per 24 h	8	410	197	—	—	1·62* (1·05, 2·20)	23·79	0·001
Need for night defaecation	4	170	122	44·1	8·2	6·64 (2·99, 14·74)	0·43	0·93
Incontinence during night	6	415	286	20·9	3·8	8·03 (4·22, 15·25)	2·11	0·83
Incontinence during day or night	6	218	281	50·5	29·9	2·71 (1·81, 4·07)	4·12	0·53
Faecal urgency	5	226	169	14·2	39·1	0·43 (0·23, 0·80)	4·35	0·36
Pad use day or night	4	117	92	15·4	5·4	2·72 (1·02, 7·23)	0·45	0·93
Quality of life								
Social restriction	2	58	85	13·7	3·5	6·04 (1·53, 23·78)	0·02	0·89

*OR, odds ratio; WMD, weighted mean difference.

2.6.4 Risk of rectal cancer and secondary proctectomy after IRA

The risk of rectal cancer after IRA remains. Several risk factors for rectal cancer have been presented, these include: high density of colorectal polyps 500 or more, rectal polyp count over 20, patient's older age, or patients' age younger than 25 at the time of surgery, the length of the retained rectal stump, colon cancer at the initial operation and inadequate rectal surveillance (Gingold et al. 1981, De Cosse et al. 1992, Bertario et al. 2000, Sinha et al. 2010). More recently, a high risk site of *APC* mutation have been added to this list of risk factors (Bertario et al. 2000, Sinha et al. 2010). The rectum must be annually surveyed by endoscopy, and despite the annual endoscopy some polyps might still develop into cancer during the surveillance interval. The overall rectal cancer risk after colectomy and IRA is reported to be 6-14% (Iwama et al. 1994, Heiskanen et al. 1997, Bülow et al. 2000, Aziz et al. 2006). The risk increases with the lengthening follow-up time. The long-term risk estimates vary and reach up to 24% at 15 years and 32% at 40 years after IRA (Iwama et al. 1994, Heiskanen et al. 1997, Bülow et al. 2000): these numbers are partly from the pre-IPAA era. During the IPAA era, the rectal cancer risk of IRA procedure has diminished perhaps mostly because of right patient selection for the both operations (Church et al. 2003). The cumulative 5-year survival for rectal cancer after colectomy and IRA is 60% (Bülow et al. 2000). Even if the rectal cancer risk is the major indication for the secondary proctectomy, not all patients have cancer at the actual time of surgery. Many patients have a worsening rectal polyposis, which makes endoscopic surveillance difficult and unreliable. Therefore, the secondary proctectomy rates are much higher than actual cancer numbers. The risk of secondary proctectomy is reported to be around 30% and the cancer detected in secondary proctectomy specimen is about 30%, respectively (Björk et al. 2000, Sinha et al. 2010). The estimated cumulative risk of secondary proctectomy, including the pre-IPAA era, is estimated to be around 70% over 30 to 40 years (Heiskanen et al. 1997, Bülow et al. 2000). The secondary proctectomy during the IPAA era, which began in 1992 accounts for only a little over 10% of the IRA patients, and the cumulative risk at 10 years is 16% (Bülow et al. 2008). The figures with a very long follow-up after the introduction of IPAA are therefore still lacking.

If the secondary proctectomy has to be carried out, the aim is to preserve the anus and to perform secondary ileal pouch-anal anastomosis. The secondary IPAA may be a technically more challenging operation due to the adhesions and sometimes, mesenteric desmoid occurrence within the operating area (Bülow et al. 2000). Mesenteric desmoid sometimes prevents the reconstruction of ileal reservoir and ileoanal anastomosis. The

intraoperative technical difficulties that prevent ileal-pouch formation affect 8-10% of cases (Penna et al. 1993, von Roon et al 2008). It has not been congruently shown if there are more complications in secondary IPAA (Bülow et al. 2000, Björk et al. 2001).

If the secondary IPAA procedure is successful, then the long term outcome is as good as with the primary IPAA. Secondary IPAA failures occur at the same frequency as in primary IPAA (Bülow et al. 2013).

2.6.5 Surveillance after colorectal surgery

All the patients need surveillance after prophylactic colorectal surgery. The rectal cancer risk is such that an annual endoscopy of the rectal stump is indicated for patients, who had undergone IRA. Rectal cancer will arise amongst a certain portion of patients in spite of annual surveillance, but the purpose of surveillance is to detect precancerous lesions in advance or at least cancer at its earliest stage so that curative treatment is still feasible and available.

The ileal pouch created during IPAA procedure is prone to adenoma formation (Beart et al. 1982). The incidence of adenomas among FAP patients in the ileal pouch varies from 7% to 74% depending on the study. The cumulative risk ranges are 7% to 16% after 5 years, 35% to 42% after 10 years, and 75% after 15 years (Friederich et al. 2008, Tajika et al. 2013). Although the rate of adenomas has shown to be quite high, the cancer risk is still low. The 10 year-cumulative-risk of pouch cancer was no more than 1% (Friederich et al. 2008). Nevertheless, regular pouch surveillance is advised for all FAP patients with IPAA (Mc Launghlin et al. 2009).

The surveillance of upper gastrointestinal polyps remains unchanged after colectomy (Spigelman et al. 1989).

2.6.6 Medical treatment

Non-steroidal anti-inflammatory drugs (NSAID) have been reported to diminish the colorectal polyp formation among FAP patients (Steinbach et al. 2000). The only effective prevention of colorectal cancer is by surgery, but there are, however, some special cases, when the chemoprevention over a limited period of time could be an appropriate choice. In some patients a large intra-abdominal desmoid tumour may prevent the secondary proctectomy after colectomy and IRA and in such a case the COX-2 inhibitor, celecoxib, with the annual endoscopic removal of rectal polyps will be the only treatment option. The European Society for Medical Oncology (ESMO)

guidelines for the year 2013 states that NSAIDs can be used as adjuvant treatments when adenoma recurrence is detected after surgery (Balmana et al. 2013). Normal dosage is 200 milligrams of celecoxib twice a day. The NSAIDs, sulindac and celecoxib both have shown to reduce the adenoma burden in the rectum after IRA, and the celecoxib possibly reduces small duodenal adenomas as well (Kim et al. 2011). Notwithstanding the treatment by NSAID medication may cause polyp regression, no reduction in the progression to adenocarcinoma has been shown (Kim et al. 2011).

2.6.7 Endoscopic treatment

Endoscopic surveillance with polyp removal has been used to prevent rectal cancer after colectomy and ileorectal anastomosis. The upper gastrointestinal polyps are often removed via endoscopy. Sometimes very mild cases of AFAP can also be considered to be managed by endoscopic polyp removal only. Endoscopy may also help to postpone upcoming surgery, if the patient is reluctant to have the prophylactic operation (Ishikawa et al. 2015).

2.7 Extra-colonic manifestations of FAP

Different manifestations of FAP are presented in schematic figure (Figure 7).

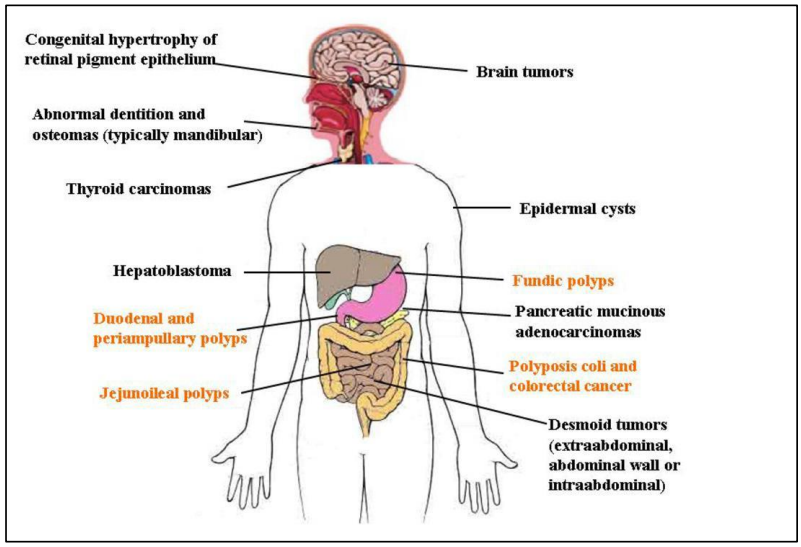


Figure 7 Manifestations of FAP, intestinal manifestations are coloured in orange and extraintestinal manifestations in black adapted from Boixadera Espax H et al. Radiologic manifestations of Gardner's syndrome (C-2191) EPOS™ poster presented at ECR 2011 by permission from the European Society of Radiology.

2.7.1 Duodenal adenomas and other intestinal adenomas

The duodenum is the second most commonly affected site in FAP (Sarre et al. 1987). The lifetime risk of duodenal adenomas for FAP patients has been reported to be virtually 100% (Heiskanen et al. 1999, Bülow et al. 2004). Duodenal adenocarcinoma is the second or third most common cause of death together with desmoid tumours. Cumulative duodenal cancer risk has been reported to be between 5% and 10% at the age of 60 years (Björk et al. 2001, Bülow et al. 2004, Lepistö et al. 2009). Even though the clinically relevant adenomas mostly occur in the duodenum, adenomas are also detected more distal to duodenum in small intestine (Alderlieste et al. 2013). The severity of duodenal polyposis has reported to be a predictor for detecting adenomas in jejunum and ileum, but advanced lesions are found rarely and only in jejunum (Ruys et al. 2010, Alderlieste et al. 2013). The polyp burden is reported to be largest in the proximal jejunum. Nevertheless, routine endoscopy beyond duodenum is not recommended. (Alderlieste et al. 2013)

Duodenal adenomatosis must be routinely followed-up among all FAP patients. Recommendations regarding the initiation of upper gastrointestinal tract endoscopies vary. Some groups suggest screening starting at the time of diagnosis and others at the ages of 25-30 years (Morburgo et al. 2004, Brosens et al. 2005, Vasen et al. 2008). Nevertheless, there is no rush to perform duodenoscopy in young FAP patients, because duodenal cancer is very rare before 30 years of age (Brosens et al. 2005). It is however recommended to perform duodenoscopy before prophylactic colectomy. The interval of the endoscopies is defined according to duodenal polyposis severity, which is defined with the Spigelman classification (Table 4 & 5) (Spigelman et al. 1989).

Table 4 *Spigelman classification for duodenal polyps*

POINTS	1	2	3
No of polyps	1-4	5-20	>20
Size of polyp (mm)	1-4	5-10	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Table 5 *The risk of duodenal cancer according to Spigelman stage.*

SPIGELMAN SCORE	STAGE	Duodenal cancer risk (%) 10 years (Groves et al. 2002)
1-4	I	0
5-6	II	2.3
7-8	III	2.4
9-12	IV	36.4

The National Comprehensive Cancer Network's (NCCN) recommendation for surveillance according to stage is: stage 0 every 4 years, stage I from 2 to 3 years, stage II from 1 to 3 years, stage III from 6 to 12 months, stage IV; no more surveillance, surgery (NCCN database). Duodenal adenomas can be treated primarily endoscopically. Large duodenal polyps can often be removed by snare excision or by endoscopic submucosal dissection technique under anesthesia. Duodenal adenomas are prone to recur after endoscopic removal. Celecoxib is used for Spigelman II and III polyposis for restraining the polyp formation (Groves et al. 2002). Surgical treatment options for duodenal adenomas are local excisions through duodenotomy, pancreas saving duodenectomy and pancreaticoduodenectomy. After duodenotomy the local recurrence rate is high, 43% in 10 years of follow-up (Farnell et al. 2000, Lepistö et al. 2009). Pylorus saving pancreaticoduodenectomy is recommended usually for stage III-IV duodenal adenomatosis and for patients with high grade dysplasia. With this treatment regimen, the occurrence of duodenal cancer was limited to 4.7% and there were no deaths due to duodenal cancer (Lepistö et al. 2009).

2.7.2 Fundic gland polyps, gastric adenomas and pyloric gland adenomas

FGPs are the most common polyps in the stomachs of FAP patients. FAP-associated FGPs are reported for up to 88% of all FAP patients (Bianchi et al. 2008, Lepistö et al. 2009). Histopathologically they are fundic glands, which are irregularly budded and cystically dilated in otherwise normal mucosa (Abraham et al. 2000). They are usually considered to be non-neoplastic; hamartomatous or hyperplastic lesions, although about 40% of FGPs have reported to have dysplasia, usually of low grade (Bertoni et al. 1999, Bianchi et al. 2008). High grade dysplasia is rare, and occurs usually in large (over one centimeter diameter) FGPs. Prophylactic gastrectomy should be considered in cases of repeated high grade dysplasia found in biopsies (Bianchi et al. 2008).

The risk of gastric adenomas is also increased among FAP patients. The incidence of adenomas has reported to be around 10% among the western FAP population. A transformation to gastric cancer is still uncommon (Biachi et al. 2008, Ngamruengphong et al. 2014).

Recently, a newly found entity, the pyloric gland adenomas, has been reported to be more common among FAP patients. Pyloric gland adenomas have been reported to occur in 6% of FAP patients whom undergo upper gastrointestinal tract endoscopy (Wood et al. 2014).

2.7.3 Desmoid tumours

Desmoid tumours are histologically benign mesenchymal tumours that arise from fibroblasts or myofibroblasts, which can be located in any part of the body. They may act aggressively when growing fast in inappropriate places. Desmoid tumours do not metastasize, however. The name aggressive fibromatosis is also used (Shields et al. 2001). Among FAP patients there is more than 800-fold the risk of desmoid tumour formation that in the general population (Nieuwenhuis et al. 2011). Other risk factors for desmoid tumours are pregnancy and previous trauma, either surgical or incidental for a desmoid area (Reitamo et al. 1986).

The median frequency of desmoid tumours among FAP patients is reported to be 10-15% and the cumulative life time risk estimates range between 14-21% (Gurbuz et al. 1994, Heiskanen et al. 1996, Soravia et al. 2000, Bertario et al. 2001, Nieuwenhuis et al. 2008, Campos et al. 2015), whereas among the general population frequency is 2-4 per million individuals (Nieuwenhuis et al. 2011, Reitamo et al. 1986). Desmoids are predominantly located in the abdominal wall or intra-abdominally in FAP patients, whereas sporadic desmoid tumours are most commonly found in the extremities. Intra-abdominal desmoid tumours occur in 10-13% of sporadic desmoids. In contrast, 51-72% of desmoids in FAP patients are intra-abdominal (Gurbuz et al. 1994, Fallen et al. 2006, Nieuwenhuis et al. 2011). FAP-related desmoids appear at younger age than sporadic desmoids (Nieuwenhuis et al. 2011). Several risk factors for desmoid tumour formation among FAP patients have been reported (Table 6).

Table 6 *Risk factors for desmoid tumours in FAP patients.*

Risk factors for desmoid tumours:
-*APC* gene mutation situated beyond codon 1444
-Positive family history of desmoid
-Prior abdominal surgery

(Bertario et al. 2001, Soravia et al. 2001, Nieuwenhuis et al. 2011)

Desmoid tumours are classified according to their location: intra-abdominal, abdominal wall or extra-abdominal. Intra-abdominal desmoids are the most difficult to treat, and these are classified as four stages: stage I for asymptomatic, non-growing desmoids; stage II for symptomatic, non-growing desmoids of 10 cm or less in maximum diameter; stage III for symptomatic desmoids of 11 to 20 cm or for asymptomatic slow-growing desmoids; and stage IV for desmoids larger than 20 cm, or rapidly growing, or with life-threatening complications (Church et al. 2005).

The symptoms of desmoid tumours are related to the site of the tumour. Desmoid tumours can obstruct the ureter or bowel when they grow intra-abdominally. Even though they are histologically benign, they are able to invade organs and the abdominal wall and thereby they cause bowel wall perforations and fistulas in the gastrointestinal and urinary tracts. The natural course of desmoid can vary. (Nieuwenhuis et al. 2011) Spontaneous regression has been reported in 10% cases of abdominal/abdominal wall desmoids (Burtenshaw et al. 2016). As much as 65% have also reported to have stable disease or regression with the 'wait-and-see' policy (Fiore et al. 2009).

2.7.4 Treatment of desmoid tumours

Surgery has been the first choice for desmoid treatment, whenever possible without major impairment of area in the question. Current desmoid tumour treatment has moved towards a more conservative management approach (Bonvalot et al. 2012, Briand et al. 2014). It is known that many desmoids remain stable or even regress, though desmoid tumour recurrences have been reported to occur in more than half of the operated patients (Mullen et al. 2012, Stoeckle et al. 2009, Briand et al. 2014). However, extra-abdominal desmoids can usually be removed surgically with clear margins and without major problems. The more problematic are the desmoid tumours in intra-abdominal location that they are usually not possible to resect with clear margins, curatively. Usually intra-abdominal desmoids are located in the mesentery. Thus, complete removal of desmoids would often demand substantial resection of the small bowel, which would predispose the patient to short bowel syndrome. The surgical treatment of desmoid has also been reported to carry a high morbidity and the recurrence rate after surgery is considerable. In general, intra-abdominal desmoid removal is not recommended, if they are asymptomatic (Kasper et al. 2011).

Desmoid tumours are prone to recur. The resection with the involved margins is a risk factor for recurrence (Mullen et al. 2012, Stoeckle et al. 2009). Some other risk factors such as the patient's young age, big tumour

size and tumour located in the extremities have been suggested for independent risk factors (Crago et al. 2013). The overall relapse rate of all desmoid tumours is 23-31%, and the 5-year recurrence free survival is 69% (Stoeckle et al. 2009, Mullen et al. 2012, Crago et al. 2013, Ihalainen et al. 2015, He et al. 2015, Burtenshaw et al. 2016). The median time for relapse has been reported to be between 14 and 22 months (Stoeckle et al. 2009, Mullen et al. 2012, Burtenshaw et al. 2016). The recurrence rate of intra-abdominal FAP-related desmoids is 22-31%, respectively (Heiskanen et al. 1996, Nieuwenhuis et al. 2011).

Radiotherapy can be used for extra-abdominal desmoid tumours as an adjuvant therapy after surgery with positive margins or as a primary therapy when the surgical resection might cause significant impairment. Radiotherapy alone or radiotherapy as an adjuvant therapy after surgery has resulted in better recurrence free survival than surgery alone (Mullen et al. 2012, Nuyttens et al. 2000). Radiotherapy has various side-effects (Tsudaka et al. 1991). The rate of the side-effects has been estimated in the long follow-up up to 26% (Guadagnolo et al. 2008). The factors that influence the risk of complications have been suspected to be high doses of radiotherapy, the patient's young age and a large area of tumour, which is subsequently treated by radiotherapy alone (Guadagnolo et al. 2008).

Some medical agents have been used to restrain the growth of the desmoid tumours, such as anti-oestrogens and NSAIDs (Soravia et al. 2000, Janinis et al. 2003). These agents have been used mostly for treating recurrent desmoids and also those tumours that cannot be resected. The recommendation is to start with NSAIDs, such as sulindac and if this fails to restrain the tumour growth by an anti-oestrogen, such as tamoxifen, and if that approach fails, then cytotoxic chemotherapy such as methotrexate or vinblastine can be considered (Janinis et al. 2003). More recently tyrosine kinase inhibitors have been introduced for desmoid disease treatment, particularly in recurrent diseases (Penel et al. 2011).

The desmoid disease shares the second place in the mortality statistics with gastroduodenal cancers in mortality because of the limited treatment options for desmoid disease (de Campos et al. 2010).

2.7.5 Other malign manifestations

In addition to colonic and upper intestinal manifestations, there are several other less frequent manifestations associated with FAP. The risk of pancreatic cancer is higher than in the general population. The relative risk has been shown to be 4.5 and the absolute lifetime risk 1.7% (Giardiello et al

1993). Pancreatic cancer is not easy to detect in its early stages and there is no routine surveillance recommended (Groen et al. 2008).

Papillary thyroid cancer is also observed more among FAP patients than control populations. The relative risk is around eight and the life time risk is 2%. Young women are particularly at risk of this condition. At least palpation of the thyroid gland is recommended yearly for young women affected, but recently ultrasound screening for thyroid cancer has also been recommended (Plair et al. 1987, Giardiello et al. 1993, Jarrar et al. 2011).

Hepatoblastoma is an embryonal liver tumour, which occurs predominantly among boys from six-months-old to three-years-old. The relative risk of hepatoblastoma in FAP families is about 850 and the absolute risk is 1.6% (Giardiello et al. 1991, Galiatsos et al. 2006). A family history of hepatoblastoma increases a risk for this rare condition. Surveillance is organized for these families and it should be started shortly after birth and continued until four years old. α-fetoprotein laboratory test and liver ultrasound should be organized every three months (Aretz et al. 2006).

Finally the association of brain tumours and FAP has been identified. This association of brain tumour and colorectal polyposis was initially called Turcot syndrome, as Turcot and colleagues were the first to describe it in 1959 (Turcot et al. 1959, Hamilton et al. 1995). The relative risk is 7 and absolute life time risk is 1-2% (Giardiello et al. 1991, Galiatsatos et al. 2006, gene reviews database). The most common type is medulloblastoma. The surveillance is not routinely recommended (Galiatsatos et al. 2006, Groen et al. 2008).

2.7.5 Other benign manifestations

Osteomas are benign osteoblastic growths. They are the most common skeletal abnormality associated with FAP. They are usually situated in the outer cortex of the skull, paranasal sinuses or the alveolus of the mandible or maxilla (Oner et al. 2006). Osteomas have been observed among 46 to 93% of FAP patients (Wijn et al. 2007). Usually they are asymptomatic. Large osteomas that restrict the movement of the jaw or are cosmetically bothersome can be removed surgically. Odontomas (9-83%), benign tumours that arise from dental tissue, and supernumerary teeth (11-27%) can be detected among FAP patients more frequently than among other population (Wijn et al. 2007). An association of osteomas and polyposis in addition to skin and soft tissue tumours such as desmoid tumours and thyroid tumours has historically been called Gardner's syndrome (Gardner et al. 1952, Järvinen et al. 1982). Of the ski manifestations epidermal cysts are the most

common (50-65%) among FAP patients (Bilkay et al. 2004). Other skin lesions include the following: lipomas, fibromas, leiomyomas, neurofibromas and pigmented skin lesions (Ascari-Raccargi et al. 1999, Bilkay et al. 2004, Burger et al. 2011).

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is a very pathognomonic feature of FAP. The condition has been reported with a specificity of up to 95% for FAP syndrome (Traboulsi et al. 1987). It is the most common extra-colonic manifestation of FAP and an early marker for it. The prevalence of CHRPE is 70-75% among FAP patients (Nieuwenhuis et al. 2007), whereas among the normal population the prevalence is only 1.2% (Coleman et al. 2007). It has no effect on the patient's sight. CHRPE is congenital therefore it can be diagnosed at any age. A patient belonging to a FAP family can theoretically be screened for CHRPE before polyps arise if the mutation of the family has not been detected (Gebert et al. 1999).

FAP patients have an increased risk of adrenal tumours. Most of the tumours are incidentalomas and are thus found during otherwise performed scanning. The risk of adrenal tumours is reported to be 7-13% (Marchesa et al. 1997, Smith et al. 2000). The clinical presentation is same as in sporadic patients. The malignant transformation is extremely rare (Barson et al. 1999).

2.8 Survival and the causes of death of FAP patients

2.8.1 Causes of death

The leading cause of death in FAP patients is still colorectal cancer, mostly among the proband population, who usually first appear with the symptoms of the colorectal cancer. Colorectal cancer deaths account for 59% to 85% of all deaths in FAP patients (Arvanitis et al. 1990, Järvinen 1992, Iwama et al. 1993, Bertario et al. 1994, de Campos et al. 2010). These high figures also include data from the era before systematic surveillance and polyposis registries were implemented. With good prophylactic surgery and early treatment of colorectal cancer the other extra-colonic manifestations related to FAP (ECMs) have become more important causes of death. The most relevant of these ECMs are the desmoid tumours and gastroduodenal cancers. The incidence of desmoid tumour deaths varies between 0-11% (Arvanitis et al. 1990, Iwama et al. 1993, Heiskanen et al. 1996, Bülow et al. 2003, Campos et al. 2010). The incidence of duodenal cancer deaths is 0-8% and gastric cancer 0-5%, respectively (Arvanitis et al. 1990, Iwama et al. 1993, Bertario et al. 1994, Belchetz et al. 1996, Heiskanen et al. 1996, Bülow

et al. 2003, Campos et al. 2010). There are also other less commonly occurring tumours related to FAP such as thyroid cancer, hepatoblastoma and brain cancer (Iwama et al. 1993, Belchetz et al. 1996). These also cause deaths occasionally. Post-operative deaths after prophylactic proctocolectomy and pancreaticoduodenectomy can also occur, though less than in early days because of better quality of perioperative care and standardized operative techniques and centralization of the surgery in high volume centers. Surgical mortality was reported in previous series to range between 0 to 5.2% (Arvanitis et al. 1990, Bertario et al. 1994, Belchetz et al. 1996 Bülow et al. 2003, Campos et al. 2010). Causes of death are reported in Table 7.

Table 7 *Causes of FAP patients' deaths in selected studies.*

			Causes of death (% of total deaths)						
Study*	**Population**	**Deaths**	**CRC**	**Desmoid**	**Duodenal + pancreas**	**Gastric**	**Other cancers**	**Perioperative**	**Other**
Arvanitis (1990)	465	110	59%	11%	8%	0%	8%	5%	9%
Vasen (1990)	230	45	64%	7%	2%	0%	0%	13%	13%
Iwama (1993)	1050	414	81%	2%	3%	3%	3%	0%	9%
Bertario (1994)	971	350	78%	4%	1%	1%	3%	0%	13%
Belchetz (1996)	461	140	74%	9%	5%	1%	5%	1%	6%
Heiskanen (2000)	236	68	79%	0%	3%	3%	0%	3%	12%
Bülow (2003)	434	175	69%	2%	3%	0%	9%	2%	15%
de Campos (2010)	97	19	63%	11%	0%	5%	5%	5%	11%
Mallinson (2010)	273	55	66%	11%	4%	2%	6%	0%	13%
Average (Weighted)	**469**	**153**	**75%**	**4%**	**3%**	**2%**	**4%**	**1%**	**11%**

* Only the first authors name given for more complete authorship see the listing in the reference section

2.8.2 Survival and the impact of registries on survival

The progression of colorectal cancer among FAP patients in earlier times was inevitable and this was also the most common cause of death. The first polyposis registry was established in St Mark's hospital in 1924 and since that time the survival of polyposis patients has improved. In general, it is recommended that all FAP patients are treated and surveyed in the context of a FAP registry. National research registry for polyposis patients in Finland was established in 1984. After the establishment of registries the incidence of CRC diminished (Järvinen 1992). Colorectal cancer mortality has also been significantly reduced (Heiskanen et al. 2000, Barrow et al. 2013). Reductions have ranged from a baseline of 44-64% to only 4-6% in colorectal cancer incidence among call-ups (Morton et al. 1993, Mallinson et al. 2010). The effect of registries and systematic screening and surveillance on overall mortality has been controversial, however. There are some studies that report significant reductions in mortality after registries, but lately controversial results that showed no improvement of overall survival have been reported (Heiskanen et al. 2000, Bülow et al. 2003, Gibbons et al. 2011). It has been suggested that when the colorectal cancer threat has been prevented, the incidence of other extra-colonic FAP-related deaths has been increased and thus the overall survival has not improved (Gibbons et al. 2011).

2.8.3 Life expectancy

Despite effective screening programmes, life expectancy among FAP patients is shortened compared to that of the general population. The life expectancy among the screened population has been reported to be 70.4 years, whereas among probands it is only 57.8 years (Mallinson et al. 2010). If the groups are put together the life expectancy among men is 63.6 and among women 66.8 years. Furthermore, if the analysis includes data obtained before 1985, then the life expectancy was 56.7 years and after 1990 it was 70.6 years. Life expectancy of the general population in same region was 78 among men and 82 among women (Wilding et al. 2012). Life expectancy of FAP patients has improved over time and is better among screened, but it is still inferior to that of the general population.

3. OBJECTIVES OF THE STUDY

The objective of this dissertation was to analyse the outcome of different operation techniques among FAP patients. The effect of screening on the survival was studied in FAP families. The association of the *APC* gene mutation and desmoid disease was studied, as were the differences between FAP-related and sporadic desmoid tumours.

The specific study aims were as follows:

1. To compare colectomy and ileorectal anastomosis (IRA) and proctocolectomy and ileal pouch-anal anastomosis (IPAA) as a treatment in FAP patients (I).

2. To determine the risk of secondary proctectomy and the risk of rectal cancer in patients, who have undergone colectomy and IRA (II).

3. To study the impact of screening on survival (III).

4. To detect the *APC* gene mutations among desmoid tumour patients (IV).

5. To compare the characteristics and the treatment of sporadic and FAP-related desmoids (V).

4. MATERIALS AND METHODS

4.1 Patients

4.1.1 A nationwide study that compared IRA and IPAA, and reports the risk of secondary proctectomy and cancer after IRA (I, II)

The prophylactic operative treatment of FAP patients by colectomies and IRA was started in Finland in 1963. The first proctocolectomy and IPAA for FAP patient was performed in 1992. Before then the options were IRA or proctocolectomy and Brooke's ileostomy. From the beginning of 1992 onwards all the Finnish FAP patients operated by IRA or IPAA were included in the Finnish polyposis registry. All the data of these patients were retrospectively collected from the polyposis registry files in addition to data of the clinical patient files. The survival information was collected from the Finnish Cancer Registry and Finnish Population Register Center. The genetic testing for FAP patients became available in Finland in the year 1996. The genetic information has since influenced the choice of the operation. Prior to the establishment of IPAA, IRA was the operation of choice for all patients who had mild or moderate polyposis with limited count of rectal polyps that could be endoscopicly removed (Table 8). After the introduction of IPAA for FAP patients, patients with moderate or severe polyposis were generally operated on with IPAA. After IRA the remaining rectum was followed-up by endoscope every year. The endpoint for survival was the date of death or the last day of the study period (30th September 2012). At the time of the last day of the study period 30th September 2012, there were a total of 228 operated patients. More than one-third 88 (39%) patients had undergone IPAA compared with 140 (61%) patients who had undergone IRA. Furthermore, these 140 IRA patients were included for further study about secondary proctectomy.

Table 8 *Indications for IRA and IPAA operations*

	Pre IPAA and pre gene testing era		IPAA era	
	C+IRA	**PC+Ileostomy**	**C+IRA**	**PC+IPAA**
Rectal polyp count	Low	High	<5 polyps	>20 polyps [1)]
Rectal cancer	No	Yes	No	Yes
Familial phenotype	Mild/moderate	Profuse	Mild	Moderate/profuse [2)]
Personal preferences	Annual follow-up, possible future proctectomy	Permanent stomy, one step operation	Annual follow-up, possible future proctectomy	To avoid annual rectoscopies, one step operation
Desmoid tumour			May prevent future IPAA	Preferable [3)]
Comorbidity	Safe	Safe	Safe	More complications [4)]
AFAP	Preferable		Preferable [3)]	
Mutation	-	-	Low risk site	High risk site [2)]

1) Church et al. 2001, 2) Wu et al. 1998, 3) Vasen et al. 2008, 4) Campos et al. 2009

4.1.2 Study of the effect of screening (III)

The nationwide study of 154 families with at least one FAP patient comprised a total of 421 patients. Two of these 421 patients were excluded: one because the diagnosis of FAP was confirmed after death and another because of missing follow-up information. The data from the year 1963 until end of the study period on April 30th 2015, were collected. Patients were divided between probands and call-ups. Probands were found because they manifested symptoms and the call-ups were their relatives, whom had been invited for a screening during which FAP was found.

4.1.3 Association of desmoid tumours and an *APC* gene mutation and comparison of sporadic and FAP-related desmoids (IV, V)

The data of the desmoid tumour patients from the year 1980 to the 30th April 2015 were collected from the database of the Department of Pathology, Helsinki University Hospital. A total of 221 patients were identified as having desmoid tumour in any part of the body. Patients between the years 2000 to 2012 were included in the prospective part of the study, which was carried in 2013. The data were collected from the patient files. The prospective phase of the study included 106 patients. Twenty-one of these patients had already undergone endoscopic FAP screening. The remaining 85 were invited to a screening. In the end total of 52 (61% of all invited patients) patients participated in the FAP screening. Of these 52 patients five had recently undergone endoscopy and they did not participate in the endoscopy part of

the screening. All patients met a colorectal surgeon with experience of hereditary colorectal cancer who gave each an information about the gene test, performed a sigmoidoscopy and asked each patient for a written consent for genetic testing. *APC* germline mutation testing was conducted first by standard exon-specific sequencing for point mutations. If a negative result of the test was received the MLPA test was conducted with the intention of finding large rearrangements. MLPA testing was carried out in the Department of Medical Genetics of Helsinki University.

Further retrospective analyses comprised all 221 desmoid tumour patients. Patient and tumour characteristics were analyzed and these were: tumour size and location, treatment, the margin status of the spesimens, recurrences, median follow-up time, age at diagnosis and the recurrence free survival. *APC* gene mutations among the FAP patients were recorded if known. Only those patients with primarily R0 or R1 resection were included in the dataset for the recurrence free survival analysis.

4.1.4 Ethical aspects

The operative ethics committee of Helsinki University Hospital approved all the parts (I-V) of this study. For the prospective part of the study (study IV) a written informed consent was obtained from every patient before taking a blood draw for genetic testing or endoscopy. The FAP research registry has obtained a research permit from the Ministry of Social Affairs and Health (No 1922/69/86) and the permit has recently been renewed in National Institute for Health and Welfare (Dno THL/1068/5.05.00/2015). All FAP patients have given written informed consent for mutation testing at the time of mutation testing, also outside of this study. Relatives have not been contacted without the permission of the proband. All families with a suspected hereditary disposition have been offered information about the gene test and the possibility for further diagnostics and treatment.

4.2 Scoring systems

A Clavien-Dindo classification was used for grading the complications. This classification categorizes the surgical complications from grades 1 to 5 according to invasiveness of the action required to treat the complication (Table 9).

Table 9 *Clavien-Dindo classification*

Grade	Definition
0	No complication
1	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic or radiological interventions.
2	The complication requiring pharmacological treatment.
3a	Surgical, endoscopic, or radiological intervention required that is not done under general anaesthesia.
3b	Surgical, endoscopic, radiological intervention done under general anaesthesia
4	Life threatening complication requiring intensive care unit management, multi-organ dysfunction
5	Death

(Dindo et al. 2004)

The classification of American Society of Anaesthesiologists (ASA) was used for assessing the patients' clinical condition and comorbidies, and the patient related risks of the surgery. Patients were classified into three categories ASA 1, ASA 2 or ASA 3 and above. ASA 1 refers to a normal healthy patient, ASA 2 to patient with mild systemic disease, and ASA 3 patient with severe systemic disease.

The extent of desmoid tumour resection was defined thus, the margin status was classified as no residual tumour (R0), microscopic residual tumour (R1) or macroscopic residual tumour (R2) according to the American Joint Committee on Cancer (AJCC) criteria, 7th edition (Edge et al. 2010).

4.3 Statistical analyses

4.3.1 I-II and IV-V

We used Kaplan-Meier survivorship curve analysis to evaluate the cumulative overall survival (I, II, V). The differences in survival curves were assessed by a log rank test. Proportions of events were compared by Pearson exact chi square, Fisher's exact tests and 2-tailed tests were used. The p-values below 0.05 were considered statistically significant. The independent samples t-test was used for comparing the differences between two groups that were continuous and normally distributed. The Mann-Whitney U test was used to compare the distributions between two groups as ordinal variables. When we studied the factors possibly affecting the survival multivariate Cox regression analysis was used (I). The factors studied were ASA classification, mutation type, histology, and rectal cancer. Factors with $p<0.1$ in the Kaplan Meier analyses were included in the Cox analysis; all parameters except the mutation type fulfilled this criterion. Cox analysis was adjusted for age, sex, and hospital type. No significant interactions were

found when the interaction terms were tested. Time dependent covariate was included separately for each testable variable for testing the Cox model assumption of constant hazard rations over time. All included variables fulfilled the Cox model assumption. Statistical analyses were performed using SPSS software (IBM Corp., New York, NY).

4.3.2 III

We compared survival and mortality between probands and call-ups. The follow-up started from the day of the diagnosis of the probands and for the called-up patients from the day they attended the first screening. The end of the study period was either death or the last day of the study period, April 30th 2015. The crude mortality rate and the number of deaths in a patient population within a year per 1000 of population counted at midyear were reported. The mortality ratio between two groups was calculated and recorded. Mortality rates were compared to the general Finnish population at the same age, standardized mortality ratio (SMR). SMR was counted separately for probands and call-ups. Rates and rate ratios were calculated using standard Poisson regression with log-link. Relative survival was estimated using the method introduced by Ederer (Ederer II). The relative survival is the ratio of the observed survival of a FAP patients compared to the expected survival of a comparable cohort of FAP free individuals or in this study the general population at the same age and of the same sex (Ederer et al. 1959, Hakulinen et al. 2011).

5. RESULTS

5.1 Comparison of IRA and IPAA (I, II)

5.1.1 Surgical Outcomes

A total of 228 FAP patients underwent IRA or IPAA operation. Of the 140 IRA patients, 49 were performed after the IPAA procedure had become an available option for FAP patients, thus 91 IRAs were performed before 1992. Furthermore 39 of the IRA operated patients underwent a secondary proctectomy. The patient characteristics are presented in Table 10.

Table 10 *Characteristics of patients who had undergone an operation*

Variable	IRA	IPAA	Secondary proctectomy
N	140	88	39
Gender, F:M	81:59	39:49	24:15
Age at operation Mean (SD)	36 (14)	30 (12)	45 (11)
Follow-up time after operation Median years (IQR)	20.7 (7.7-27.4)	9.7 (4.6-15.6)	10.3 (2.2-14.7)
Proband:call-up	58:82	28:60	16:23
Expression type FAP:AFAP	123:17	85:3	37:2

The diagnosis of FAP was made by endoscopy for 204 (89%) of patients, most of which were done before the genetic testing had become available. There were six patients in the IRA group whom had a mutation in a high risk site (codon 1250-1464) and whom were operated before the genetic testing or IPAA procedure were available. After IPAA was introduced among FAP patients in Finland all eight high risk mutation patients were operated on by IPAA. The ASA classes of the patients at the time of IRA and IPAA are presented in Table 11.

Table 11 *ASA classes of the IRA and IPAA operated patients*

Variable	IRA	IPAA
ASA class:		
ASA1	87 (62%)	54 (61%)
ASA2	30 (21%)	26 (30%)
ASA3 or more	10 (7%)	2 (2%)
No data	13 (9%)	6 (7%)

Mann-Whitney U p=NS

The median hospitalization time was nine days for the entire IRA group and from the year 1992 on it was eight days. Hospitalization time for the IPAA group was also nine days. Complications were detected in 28 (21%) of 135 patients in the IRA group (data was missing in five cases), whereas 26 (30%) of 87 patients in IPAA group had complications (data missing in one case) (Table 12).

Table 12 *The severity of complications and specific complications after IRA and IPAA operations*

Complication	IRA	IRA after 1992 (included also in IRA)	IPAA
Clavien-Dindo class:			
1	11 (8%)	5 (10%)	8 (9%)
2	1 (1%)	0	10 (11%)
3a	1 (1%)	1 (2%)	3 (3%)
3b	13 (10%)	4 (8%)	5 (6%)
4	1 (1%)	1 (2%)	0
5	1 (1%)	0	0
Specific complications:			
Wound infection	1 (1%)	1 (2%)	2 (2%)
Abscess	4 (3%)	0	3 (3%)
Leakage	9 (6%)	4 (8%)	2 (2%)
Haemorrhage	1 (1%)	0	5 (6%)
Ileus	3 (2%)	1 (2%)	2 (2%)
Other postoperative	9 (6%)	5 (10%)	12 (14%)
Post operative death (within 30 days)	1 (1%)	0	0
Total	28 (21%)	11 (22%)	26 (30%)

Mann-Whitney U of Clavien-Dindo class p=NS

There were no differences in the overall complication rates between the groups (p=NS). There were tendency toward more severe complications

(Clavien-Dindo ≥3b) in the IRA group compared to the IPAA group; 15 (11%) vs. 5 (6%). This same tendency in complications was seen when IRA operations were performed in the IPAA era, five (10%) in IRA group. Complications were associated with a higher ASA classes (ASA class 1, 19%: ASA class 2, 36%: ASA class 3–4, 33% p = 0.04). Re-operations due to complications within 30 days were performed for 13 (9.6%) patients of the IRA group, for four (8.2%) patients operated by IRA from the year 1992 onwards and for six (6.9%) of 87 patients of the IPAA group. There were 23 (16%) cancers detected in IRA specimens and severe dysplasia was found in 13 (9%) specimens. Among IPAA operation there were 11 (13%) cancers and 19 (22%) severe dysplasias. In rest of the specimens, there were mild dysplasia or no dysplasia.

Altogether 39 (28%) of patients in the IRA group underwent secondary proctectomy a median of 14 years after the primary operation. The cumulative risk for secondary proctectomy was 5% at five years, 30% at 20 years and 53% at 30 years after the primary operation (Figure 8).

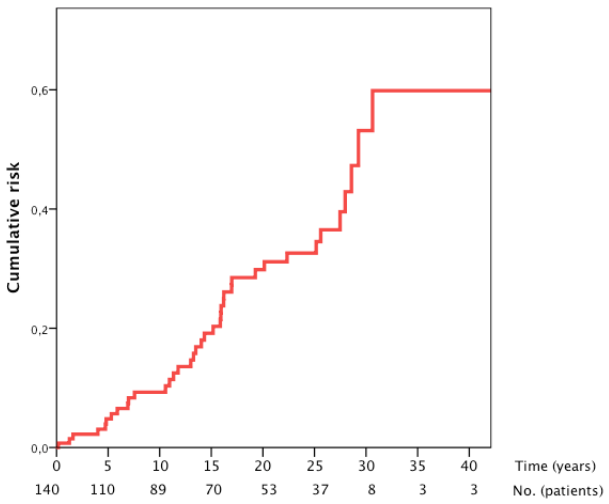


Figure 8 Cumulative risk of secondary proctectomy after IRA.

There were 24 (62%) secondary proctectomies done initially with IPAA, but five (21%) of these 24 pouches were finally converted to permanent ileostomies. Two of these were performed because of postoperative haemorrhage and leakage and three because of chronic anal incontinence. A total of 21 (15%) of patients with IRA finally ended up with permanent ileostomy. The median time for ileostomy after IRA was 16 years. The ileal pouch was removed and converted to ileostomy in three (3.4%) patients. The

median time for ileostomy after the IPAA procedure was 2.4 years. Two AFAP patients underwent secondary proctectomy, and both of these were because of profuse polyposis. The reasons for secondary proctectomies and permanent ileostomies performed in connection with secondary proctectomies are presented in Table 13.

Table 13 *Indications for secondary proctectomies and permanent ileostomies in secondary proctectomy operation.*

Indications for secondary proctectomy	Number (%)	Indications for permanent ileostomy	Number (%)
Cancer or suspicion of cancer	17 (44%)	Before the IPAA era	7 (33%)
Profuse polyposis	17(44%)	Distal rectal cancer	4 (19%)
Anal incontinence	2 (5%)	Mesenteric desmoid	2 (10%)
Patients wish	3 (8%)	Patients wish	3 (14%)
		Failed IPAA	5 (24%)
Total	39 (100%)	Total	21 (100%)

A total of 48 proctocolectomies with ileostomy were initially performed without an attempt to save the anus. Sixteen of these were carried out after the introduction of the IPAA technique. The indication for proctocolectomy with permanent ileostomy before the year 1992 was rectal cancer in 18 patients and severe polyposis in 14 patients. After 1992, low rectal cancer was the indication for permanent ileostomy in 11 patients and severe polyposis in 5 patients.

5.1.2 Rectal cancer rate and survival after the primary operation

The median follow-up time after IRA was significantly longer than after IPAA (20.7 vs. 9.7 years, $p<0.001$). There were 18 (13%) patients diagnosed with postoperative rectal cancer. All of these cancers were in the IRA group. The mean time for rectal cancer occurrence after IRA was 16 years. There were six proctectomies with IPAA and six proctectomies with ileostomy performed because of rectal cancer. No rectal cancers were detected among the AFAP patients. There were no cases of rectal or ileal pouch cancer in the primary IPAA group. The cumulative risk of rectal cancer was 3% at 5 years and 5% at 15 years (Figure 9), but from the year 1992 onwards the cumulative risk for operated patients was 0 until 15 years.

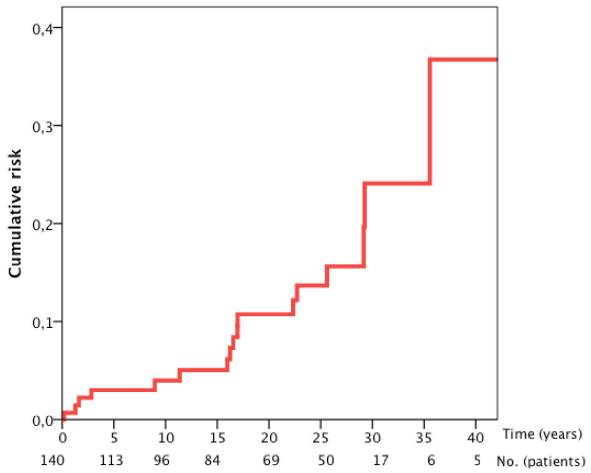


Figure 9 Cumulative risk of rectal cancer after IRA operation.

Rectal cancer deaths were detected in 10 patients, which equates to a rectal cancer mortality of 7%. There was no rectal cancer related deaths after IPAA era operated IRAs. The five years survival rate after rectal cancer diagnosis was 55%. Cumulative risk of death of rectal cancer after IRA was 2% at 5 years and 3% at 15 years (Figure 10).

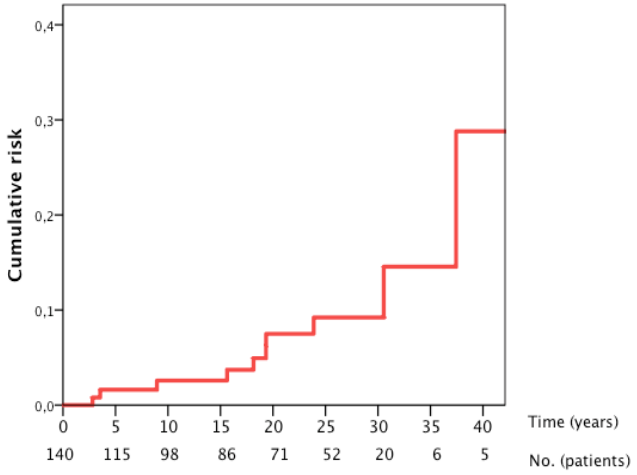


Figure 10 Cumulative risk of rectal cancer death after IRA operation.

The overall survival was lower after IRA than after IPAA (p=0.03): 88% vs. 96% at 10 years, and 84% vs. 96% at 15 years (Figure 11). There was no significant difference in overall survival (p=0.06) between IRA and IPAA groups after IPAA technique was adopted though there is a tendency toward better survival in the IPAA group (Figure 12). The age-specific survival was also lower after IRA than after IPAA (p=0.003): 98% vs. 98% at 30 years, 93% vs. 98% at 40 years, 86% vs. 98% at 50 years, and 73% vs. 89% years at 60 years of age.

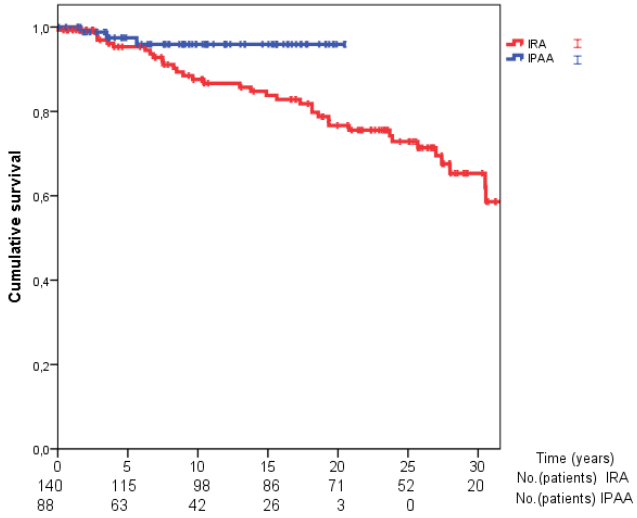


Figure 11 Cumulative survival after IRA and IPAA operations.

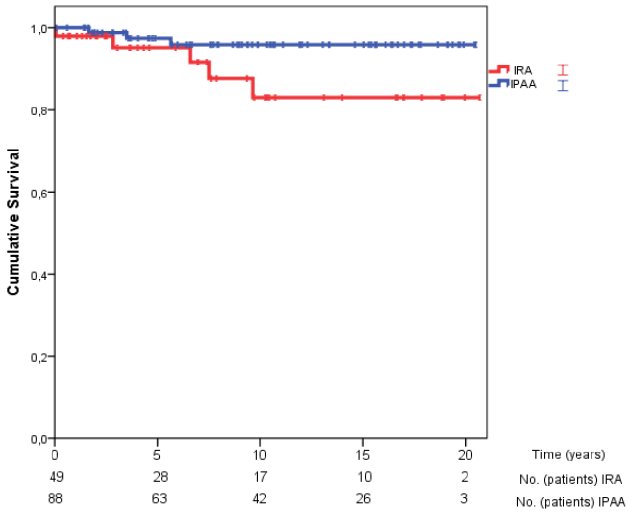


Figure 12 Cumulative survival after IRA and IPAA operations from the year 1992.

Cox regression analysis revealed that patients with higher ASA classifications had a worse survival (ASA 3: HR 5.3, 95%CI: 1.3-22, p=0.02). Postoperative rectal cancer reached significance as an independent risk factor as well (HR 2.4, 95%CI: 1.0-5.6, p=0.046). The histology of specimen (benign, high grade dysplasia or cancer) did not reach statistical significance as an independent risk factor.

Causes of death among IRA and IPAA operated patients are presented in Table 14. All the rectal cancer deaths were among IRA patients operated before the IPAA era. In attenuated FAP patients (17 with IRA and 3 with IPAA) there were no cancer-related deaths. From the 1992 onwards operated IRA patients there were three deaths: one gastric cancer related death, one desmoid tumour related death and one non-FAP related cancer death.

Table 14 *Causes of deaths after the operation*

Cause	IRA	IPAA	p-value
Rectal cancer	10 (7%)	0	0.02
Colon cancer	2 (1%)	0	NS
Duodenal or pancreatic cancer	4 (3%)	0	NS
Gastric cancer	2 (1%)	1 (1%)	NS
Desmoid tumor	3 (2%)	1 (1%)	NS
Postoperative death	1 (1%)	0	NS
Other cancer	3 (2%)	1 (%)	NS
Other	14 (10%)	0	0.003
Total	39 (33%)	3 (3%)	<0.001

5.2 Survival differences between call-ups and probands (III)

A total of 194 probands were found. Among the call-ups, initially 83 patients were diagnosed by a gene mutation test, and 142 patients were diagnosed by endoscopy. All had undergone endoscopy afterwards. Among the currently alive Finnish FAP patients 274 (92%) of 297 belong to families with a known mutation. Patient characteristics are presented in Table 15.

Table 15 *Characteristics of all FAP patients.*

	Probands	Call-ups	Total
Patients (No)	194	225	419
Gender F:M	116:78	106:119	222:197
Age at diagnosis (Mean, SD)	39 (14)	27 (15)	33 (16)
Follow-up time years (Median, IQR)	9 (3-24)	14 (7-24)	12 (4-24)

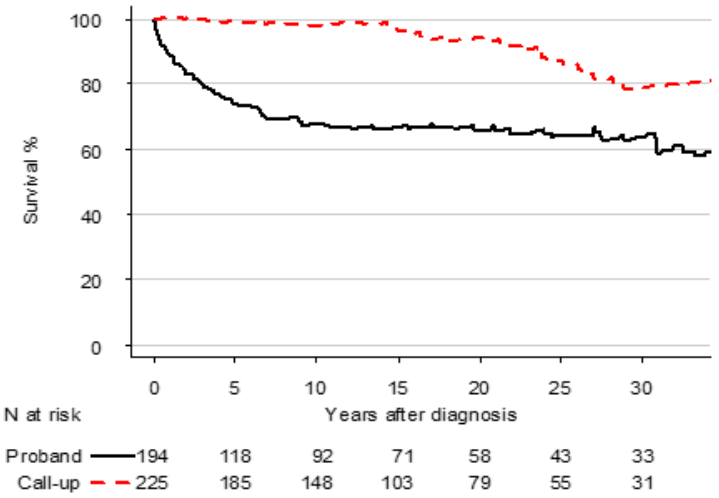
Mortality rates are reported in Table 16 with their 95% confidence intervals (CIs). There was a difference in mortality rates between probands and call-ups. There was also a difference in total SMR. The SMR in the proband group was elevated at the beginning of the follow-up and then after 10 years it decreased slowly. The SMR remained at about 2 for the call-ups until 20 years after diagnosis.

Table 16 *Crude mortality and standard mortality ratios according to group at 95% confidence intervals.*

	Probands (95% CI)	Call-ups (95% CI)
Patients	194	225
Deaths	92	30
Crude mortality rate	34.9 (28.4-42.8)	8.3 (5.8-11.8)
Risk ratio (95%CI)	1.0	0.24 (0.16-0.36)
SMR 0 years (95%CI)	16.4 (12.3-21.3)	1.65 (0.51-3.82)
SMR 5 years (95%CI)	5.00 (2.75-8.24)	2.07 (0.64-4.82)
SMR 10 years (95%CI)	1.44 (0.45-3.35)	2.16 (0.67-5.03)
SMR 20 years (95%CI)	1.79 (0.64-3.85)	4.35 (1.87-8.41)
SMR 30 years (95%CI)	2.18 (1.13-3.74)	0.68 (0.04-2.98)
Total SMR (95%CI)	4.07 (3.29-4.96)#	2.47 (1.69-3.46)

SMR=standardized mortality ratio, #Testing SMR (Proband) vs. SMR(Call-up) p=0.014

The relative survival for probands was lower than for the call-ups ($p<0.001$). Relative survival for call-ups remained at the approximate level to that of the general population up to 20 years after the initial diagnosis. The relative survival for the proband group was 67% after 10 years after diagnosis (Figure 13).



Years		5	10	15	20	25	30
Relative survival	Proband	74%	67%	67%	66%	64%	64%
	Call-up	99%	98%	96%	94%	87%	79%

Figure 13 Relative survival compared to comparable population

Causes of deaths and median ages at death for both probands and call-ups groups are listed in Table 17. There were a total of 122 deaths during the follow-up time. The FAP-related causes were the predominant reason for the deaths. As much as, 52% (64 of 122) of FAP patients died of colorectal cancer, 11% died of other FAP-related cancers, 3.3% from desmoid related deaths and 2.5% died of post-operative complications. The proband groups had significantly ($p<0.001$) more deaths due to colorectal cancer than their call-up counterparts. There were no differences between the groups for extra-colonic FAP-related deaths (p=NS).

Table 17 *Death causes of all FAP patients.*

Death cause	Median age	Number of deaths (%)	Median age	Number of deaths (%)
	Probands n=194		Call-ups n=225	
Colorectal cancer	47.4	56 (61)	58.9	8 (27)
Pancreatic/duodenal cancer	60.3	5 (5)	51.9	4 (13)
Gastric cancer	54.5	3 (3)	29.2	1 (3)
Post-operative complication	53.7	3 (3)		0 (0)
Desmoid tumour	26.1	1 (1)	37.2	3 (10)
Medulloblastoma		0 (0)	22.4	1 (3)
Other cancer	55.6	6 (7)	57.7	3 (10)
Other or unknown	68.9	18 (20)	58.2	10 (33)
Total	53.7	92 (100)	56.2	30 (100)

5.3 *APC* gene mutation in desmoid tumour patients (IV)

There were 13 (12%) FAP patients among 106 patients with desmoid tumours. Ten of these desmoid patients had FAP diagnosis before the desmoid disease manifested, but the remaining three had a desmoid diagnosis first and the FAP screening was carried out because of this diagnosis. All three of these FAP patients had endoscopy first, then the *APC* gene mutation was subsequently found. The mutations were found in exon 8 codon 283, exon 15 codon 1547 and exon 15 codon 2004 of the gene. During prospective study 52 patients underwent *APC* gene mutation testing and 45 of them also had sigmoidoscopy. There were no new FAP cases found upon the endoscopy or in the gene mutation testing in addition to the three cases that already had identified mutations. Thus the overall *APC* mutation rate for initially sporadic desmoid patients was 4.8% (3/63). Two variants of unknown significance in the *APC* gene were found among the tested patients. The study process is illustrated in Figure 14.

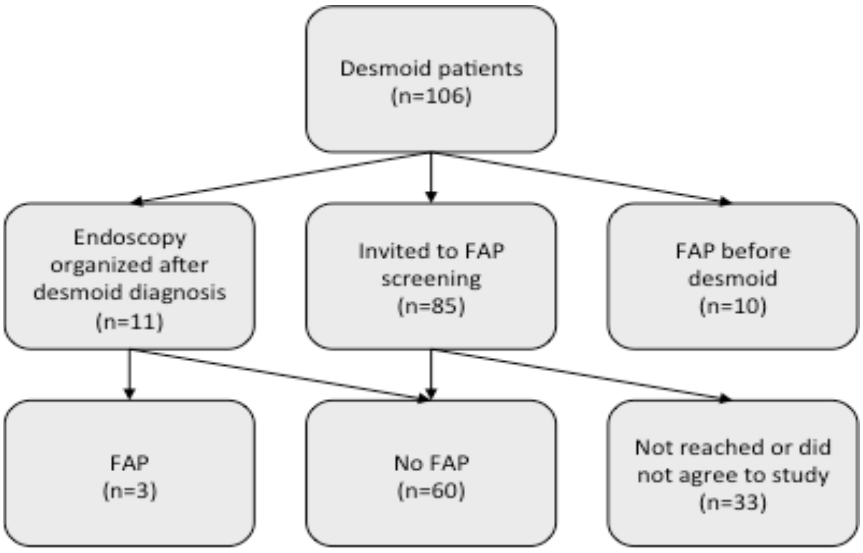


Figure 14 Flowchart about prospective study protocol and results.

5.4 Comparison of sporadic and FAP-related desmoid tumours (IV, V)

At the time of their diagnosis the FAP patients were predominantly younger than those patients with the sporadic disease, and the gender distribution was equal among them. All the desmoids among the 22 FAP-related desmoid tumour patients were located intra-abdominally or in the abdominal wall. Among sporadic counterparts the location of the desmoids was mostly elsewhere (other truncal or extremities). There were 16 patients who had multiple desmoids, 12 of which were in the FAP desmoid group. The patients in the sporadic desmoid group were predominantly females who were about 10 years older than those of the FAP group. The desmoids of the sporadic desmoid group were situated mostly in the abdominal wall or other locations (Table 18).

Table 18 *Comparison of sporadic and FAP-related desmoids.*

Variable	Sporadic desmoid N=199	FAP + desmoid N=22	P-value
Female / male	145 / 54	10 / 12	0.008
Age at diagnosis (years), mean (SD)	42.4 (16.4)	30.5 (9.9)	0.001
Desmoid location			
- **abdominal, at least**	26	15	<0.001
- **abdominal wall**	70	7	NS
- **other**	103	0	<0.001
Size of the biggest desmoid			
- **<5 cm**	72	1	0.002
- **5-10 cm**	79	3	0.019
- **>10 cm**	42	15	<0.001
No data	6	3	
Multiple desmoids	4	12	<0.001
Death to desmoid tumour	0	3	<0.001

5.5 Treatment of sporadic and FAP-related desmoid tumours (V)

Previous pregnancy, surgery or other trauma preceded the 39% of sporadic desmoids and 64% in FAP desmoids. A total of 198 (90%) patients were given surgical treatment (Table 19). There were no data available on the treatment of one of the 221 desmoid tumour patients. Noninvolved margins were more common in the sporadic group, whereas half of the operations in FAP-related desmoid group were intralesional. Half of the 18 intralesional operations did not require any further treatment during the follow-up time. Six patients received adjuvant medical therapy and 17 patients received adjuvant radiotherapy. All the patients with adjuvant medical therapy had FAP. Radiotherapy was given as the first treatment to nine (4.6%) of all patients. Two of these nine patients also had medical therapy. Regression or stable diseases was noted in six patients of the sporadic desmoid group after receiving irradiation treatment. There was a wide variation in medical agents used: thyrosine kinase inhibitors, immunosuppressants, anti-oestrogens and cytostatic agents. Fourteen patients were initially treated according to the wait-and-see strategy. None of these were subsequently operated.

Table 19 *Surgery and recurrences.*

Variable	Sporadic desmoid 198	FAP-related desmoid 22	p-value
Surgery	179	18	NS
- **R0**	99	5	0.048
- **R1**	67	4	NS
- **R2**	9	9	<0.001
- **no data available**	4		
Recurrence after operation	42	4	NS
Mean time in years	2.42 (SD 3.69)	2.18 (SD 0.99)	NS
Recurrences after primary resection being:			
- **R0**	13 (13%)	2 (40%)	NS
- **R1**	27 (40%)	2 (50%)	NS
- **no data**	2		

Recurrences were detected in 42 (25%) of sporadic desmoid patients and in four (44%) of FAP patients who initially had their tumours completely removed. R0 resected tumours recurred in 15 (14%) cases and R1 in 29 (41%) cases. The mean time for recurrences to occur was two years. Of the 46 recurrences, 31 (67%) were treated surgically, 9 (20%) by radiotherapy and 4 (9%) were only followed-up (there are no data available on the treatment of 2 (4%) recurrences).

FAP-related desmoids caused death in three cases. There were no deaths related to sporadic desmoids. Sixteen patients of the FAP-related desmoids had a known point mutation in the *APC* gene. Half of these mutations were situated after codon 1444.

6. DISCUSSION

6.1 IRA and IPAA (I, II)

The overall survival of operated FAP patients was better for the proctocolectomy and IPAA groups than for the colectomy and IRA groups. The overall survival of IRA operated patients was diminished mainly because of deaths related to rectal cancer. There were no rectal cancer deaths detected for the IRA patients, who had been operated after the IPAA era commenced in 1992. Among AFAP patients there were no rectal cancers detected after IRA operation.

Postoperative morbidity rates were 21% for the IRA group and 30% for the IPAA group. Re-operations were done for 9.6% after IRA and for 6.9% of patients after IPAA. These differences in morbidity or reoperation rates were not significant, however. Previous studies that compared IRA and IPAA complication rates have hitherto been very inconsistent. IRA related complications have been reported to range from 0% to 28% of operations whereas those of IPAA related complications from 10% to as high as 60% of the operations (Madden et al. 1991, Ambroze et al. 1992, Tonelli et al. 1997, Soravia et al. 1999, Björk et al. 2001, Günther et al. 2003, Campos et al. 2009). Generally these studies reported more complications and reoperations after IPAA. The overall complication rates reported in a meta-analysis that compared IRA and IPAA operations did not reach statistical significance, but the reoperation rates were significantly different 23% for IPAA vs. 12% for IRA (Aziz et al. 2006). Our morbidity rates are close to the median of these previously reported figures even if our complication rate and reoperation rate was not bigger after IPAA. The reoperation rate in our cohort was clearly less than found in the meta-analysis. There was a tendency in our study towards more severe complications in the IRA group (Clavien-Dindo >3b). This same difference remained when taking into account operated IRA patients prior to 1992. This is somewhat surprising, because IRA has been regarded as an easier procedure in general. In IRA group there were more leakages, which is an unexpected outcome, too. The higher incidence of these severe complications in our IRA group might be explained by the fact that the patients in the IRA group were older than those of the IPAA. Although all of the patients were young compared to general age of colorectal patients. In IRA group there were 7% of patients with ASA class 3 or more, where as in IPAA group only 2%, though this difference wasn't significant. In addition, some of the IRA operations were performed in the days of less developed perioperative patient care. Among IPAA patients there

were more postoperative haemorrhages and other non-surgical postoperative complications. This may be related to IPAA being generally more challenging procedure than IRA.

The risk of rectal cancer and rectal cancer death is the major concern after having IRA. It is the main determining factor on a patient's prognosis and on the need for a secondary proctectomy. Furthermore, when the secondary proctectomy is necessary, anus preservation is matter of great importance. The rectal cancer rate in our study was 13%, and the corresponding rectal cancer death rate was 7%. This is the same level as that of previously published results and when taken into account our long study period median of 21 years, it is even quite a good result. A previous meta-analysis calculated the risk of rectal cancer to be 5.5%. The median follow-up time in that study was eight years (Aziz et al. 2006). More recently, the risk of rectal cancer was found to be 11% over a median of 15 years follow-up time (Sinha et al. 2010). The cumulative rectal cancer risk has been estimated to be 17% after five years, 24% after 10 years, and 43% over 15 years (Campos et al. 2009). Those figures are far higher than the 3% at 5 years, 4% at 10 years and 5% at 15 years figures we obtained in the present study. The cumulative risk of rectal cancer death stayed relatively low within 30 years after IRA, but even if IRA had been done in patients' thirties, there was a substantial 9% risk of death due to rectal cancer at about their 60s. Our low risk of rectal cancer after IRA may indicate the successful patient selection, based on patients' phenotype, genotype, preferences and family history, and meticulous yearly follow-up. In addition majority of the patients were operated and followed-up by one experienced center and furthermore a few experienced surgeons. The rate of rectal cancer death in our study compared to rectal cancer rate indicates that the rectal cancer prognosis is no better among IRA patients compared to overall sporadic rectal cancer prognosis. This is somewhat surprising considering yearly organised endoscopic follow-up visits. In part, this may be due to the fact that before the IPAA era patients with quite profuse polyposis could also undergo IRA in order not to end up with permanent stoma. Yearly organized endoscopic visits have reported to diminish colorectal cancer mortality among call-up population (Mallinson et al. 2010).

The rectal cancer and polyposis that was uncontrollable by endoscopy were the indications for secondary proctectomy in the majority (95%) of cases in our study. A total of 28% of the IRA patients eventually had secondary proctectomy. Our follow-up time after IRA was long and indeed the risk of secondary proctectomy began to increase more than 15 years after the first surgery. The cumulative risk rate of 53% by 30 years indicates that over the half of the patients will need proctectomy during their lifetime. Another study by Sinha and colleagues reported a 29% rectal failure rate, and that by

the age of 60 years half of the patients had retained their rectum (Sinha et al. 2010). Those authors' results are in line with our results. The secondary IPAA was performed for 62%, but 5 (21%) of these patients eventually had ileostomy. Thus the anus preservation rate after IRA was finally 49% in our study. Our 21% pouch failure rate was far more than 5% pouch failure rate reported earlier when IPAA as a primary operation for ulcerative colitis and FAP (Lepistö et al. 2002, Fazio et al. 2013). This might reflect that the secondary proctectomy would be technically more demanding. Previous studies, which compared primary and secondary IPAA, reported higher frequency of intra-operative difficulties in secondary proctectomy (Penna et al. 1993, Bülow et al. 2013). In one study there were more postoperative complications after secondary proctectomy (Björk et al. 2001), whereas others have not been found differences in postoperative complications among primary and secondary proctectomy (von Roon et al. 2008, Bülow et al. 2013). However, there have not been reported differences between the cumulative five-year failure rates for primary and secondary proctectomy, 9% and 8% (von Roon et al. 2008). The most common reason for pouch failure was anal incontinence in our cohort. This same reason for pouch failure has been noted earlier in other studies (Hahnloser et al. 2007).

There were more deaths in the IRA group, and these also included not FAP-related causes. This higher death rate may reflect that the follow-up time for the IRA group was twice as long as for the IPAA group. The survival benefit of IPAA patients after 1992 was not statistically significant. This is in line with Yamaguchi and colleagues who reported no difference in survival between IRA and IPAA groups (Yamaguchi et al. 1996). This may be a result of the hopefully better patient selection after the IPAA technique was adopted. On the other hand, the median follow-up time for IRA after the IPAA era had ensued is shorter and thus there may still emerge new rectal cancers in IRA patients in the future. Some studies attempted to demonstrate the better survival in the IRA group after IPAA came available. An international study reported a rectal cancer rate of 10% in the pre IPAA era compared with only 2% in the IPAA era. However, this study did not detect a significant difference in the cumulative survival of these groups and part of the survival benefit in the IPAA era operated patients is likely to be explained by the shorter follow-up (Bülow et al. 2008), which might be the reason for better survival also in our study. Another study reported rectal cancer rates of 13% and 0% before and after the adoption of IPAA, respectively (Church et al. 2003). Nevertheless, they had the same problem as we have with shorter follow-up time for the IPAA era operated patients (Church et al. 2003). After having both operations, IRA and IPAA, patients still carry a risk of FAP-related cancer death. It will not be until we obtain data obtained over a very

long follow-up time after the adoption of IPAA, that we can draw definite conclusions about the preferable operation type for the FAP patients with mild rectal polyposis.

When choosing the operation type for an individual patient, the mutation status must also be kept in mind. Our data are partly historical from the time before the genetic testing. After IPAA and genetic testing became available in 1996, all the patients who had a high risk mutation site (codons 1250-1464) were operated on with primary IPAA. There were only two (10%) secondary proctectomies performed on patients who had AFAP and IRA operation performed earlier. Other studies have also emphasized the low risk of secondary proctectomy in the AFAP group, and a high risk with the severe genotype (Nieuwenhuis et al. 2009).

6.2 Success of screening (III)

We found in our nationwide population-based study that screening of FAP patients reduces overall mortality and improves relative survival when compared to the general Finnish population. The benefit in diminished mortality comes from the significant reduction of deaths due to colorectal cancer for the screening population who have an opportunity to undergo surgery at right time. There was no difference among call-ups and probands for other FAP related deaths (part of which are not screenable). The conclusions in earlier studies about the survival benefit of screened population have been controversial. Some studies have observed a significant difference in survival (Bülow et al. 1995, Heiskanen et al. 2000, Mallinson et al. 2010). However, one other study found there was no benefit gain in terms of overall survival when starting follow-up from birth (Gibbons et al. 2011).

We preferred to use the relative survival estimation for both groups separately to diminish the biases related to the entry of different ages to study. This method compares the survival of populations with same age and gender. Estimating the survival is prone to biases. The achievement and interpretation of survival studies can fail when the concept of the impacts of biases is not understood. The fundamental question is: What is the starting date of the follow-up when survival is estimated? Lead-time bias suggests that the natural history of the disease is not truly affected by screening. The advantage in time gained by call-ups in diagnosing the disease earlier is lost when starting follow-up at the same age. If follow-up among FAP patients is started from the first visit to the clinic, then the follow-up group without any symptoms will have a lead-time in comparison to proband group that presents with symptoms about 15-20 years later (lead time bias). Immortal time on the other hand refers to time during which the death of patient

cannot occur. If follow-up is started from the day of birth especially for a member of the proband group, then that individual will gain immortal time, which will be equal to the interval of time from the birth to the first day of the disease (immortal time bias).

We also estimated the relative survival starting from the birth to study possible biases. The survival benefit for call-ups diminished but was not entirely lost, and here immortal time bias exists for both groups when the survival before the age of 30 seems to be over 100%. Finally, we demonstrated the survival by starting the follow-up for every family from the day of the proband's entry into the clinic. This diminished the lead-time bias. With this method the survival benefit of call-ups also stayed (Figure 15).

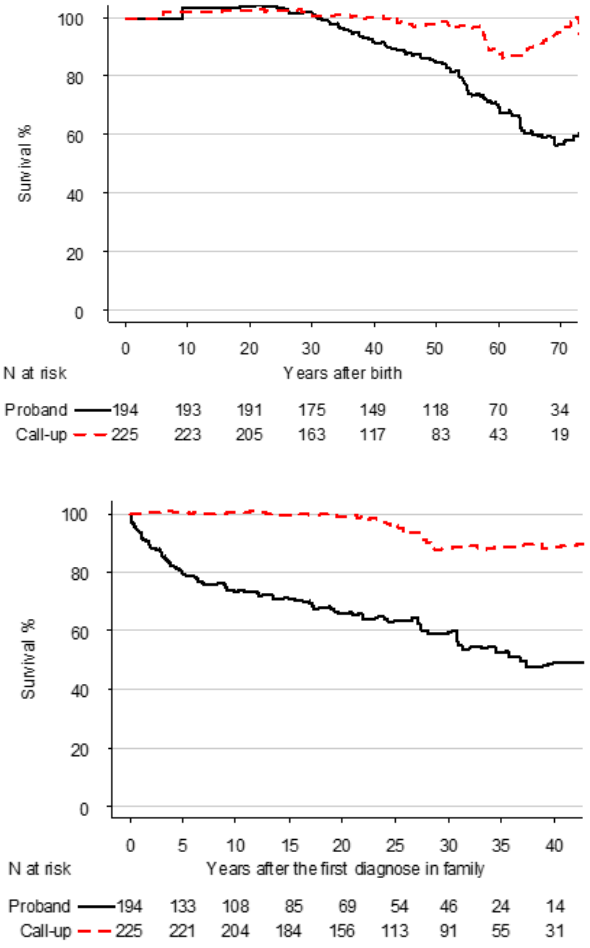


Figure 15 Relative survivals with different starting points

There were no differences between the causes of death regarding extra-colonic FAP-related deaths between these two groups. Previously, a difference in extra colonic causes in favour of probands had been reported (Gibbons et al. 2011). In total, 21 extracolonic FAP-related deaths occurred in our series, which is 17% of all deaths. Previously, reported death rates due to FAP-related extracolonic reasons have varied been 6% and 27% (Arvanitis et al. 1990, Vasen et al. 1990, Iwama et al. 1993, Bertario et al. 1994, Belchetz et al. 1996, Heiskanen et al. 2000, Bülow et al. 2003, Campos et al. 2010). Colorectal cancer was still the leading cause of death among FAP patients in earlier studies, just as it was for 52% of all patients in our cohort. Other groups have reported higher figures 59-85% for death from colorectal cancer, which perhaps reflects the higher proportion of probands in those studies (Arvanitis et al. 1990, Vasen et al. 1990, Iwama et al. 1993, Bertario et al. 1994, Belchetz et al. 1996, Heiskanen et al. 2000, Bülow et al. 2003, Campos et al. 2010).

6.3 Desmoid tumours and FAP (IV, V)

Our prospective study on FAP screening among desmoid tumour patients found no new FAP cases. There were, however, three FAP patients who had initially been diagnosed because of desmoid tumour before the screening in the present prospective study. Consequently, the risk of FAP among the initially sporadic desmoid tumour patients was 4.8% in our study.

We performed genetic testing for all patients who attended to study. Many of the previous studies are retrospective and possible FAP diagnosis had only been confirmed by endoscopy alone and in some cases this was only for symptomatic patients (Nieuwenhuis et al. 2011, Fallen et al. 2006). This approach may have missed some milder asymptomatic and possibly also almost apolypotic cases of AFAP. There are case reports that describe desmoid tumour patients with AFAP which had not been diagnosed by endoscopy because no polyps had been found at a young age, but gene mutation testing revealed an *APC* gene mutation (Bandipalliam et al. 2004, Benoit et al. 2007). A previous study about eight desmoid tumour patients with a family history of colon cancer found no *APC* germline mutations, and another study with 16 desmoid tumour patients found no *APC* mutations either (Giarola et al. 1998, Brueckl et al. 2005).

Our study on the other hand found that 10% of the 221 desmoid tumour patients had FAP. Most of them were initially diagnosed with FAP and the desmoid tumour was detected later. Previous studies reported 8-16% of desmoid tumours to be associated with FAP (Fallen et al. 2006, Nieuwenhuis

et al. 2011). There might be some underestimation of the association of FAP and desmoids for two reasons: first not the all desmoid tumour patients will have undergone sufficient FAP screening, and second not all the desmoids among FAP patients are visible via non-invasive examinations when they locate as flat lesions in the intra-abdominal region. Incidental desmoids have been reported to exist among 13% of FAP patients, who underwent laparotomy (Hartley et al. 2004). FAP associated desmoids are predominantly intra-abdominal. They are diagnosed at a younger age and have an equal gender distribution. Our data also show that FAP-related desmoid tumours are bigger, which has not been reported in previous studies (Fallen et al. 2006, Nieuwenhuis et al. 2011). Germline mutations in *APC* gene in FAP-related desmoid population tend to be located near to 3′ end of the codon, i.e. after codon 1444 (Caspari et al. 1995, Leoz et al. 2015). Proportionally more mutations were located after codon 1444 among FAP-related desmoid tumour patients than in FAP patients in general (Bertario et al. 2001, Lefevre et al. 2008).

A predisposing factor such as surgical or other trauma or pregnancy, for desmoid tumour occurred in 39% of our patients with sporadic desmoid tumours, and in 64% of those with FAP related desmoid tumours. Previous reports of predisposing factor have been reported to exist among 34% of desmoid patients (Stoeckle et al. 2009). The risk of desmoid formation among FAP patients after surgical trauma is known. For example, Clark and colleagues reported 82% of FAP desmoid patients also had predisposing surgery and 59% of female FAP desmoid patients had a predisposing pregnancy (Clark et al. 1999). It has also been demonstrated that incidental desmoids occurred in 3% of the first laparotomies, but accounted for as much as 30% in further laparotomies (Hartley et al. 2004). Nonetheless, abdominal surgery cannot be avoided among FAP patients, because of the otherwise inevitable colorectal cancer. Furthermore, when the surgery is postponed for too long due to a fear of desmoid, the desmoid tumour can also appear without surgical trauma and may even eventually prevent proctocolectomy and ileal pouch-anal anastomosis.

Resections with clear margins were more common among sporadic desmoid patients in our series and intralesional resections were more common among FAP-related desmoid patients. The most likely explanation for this is that FAP-related desmoid tumours are bigger and have more difficult locations from the perspective of their total removal. Fourteen patients in our study were only followed-up without the need to be operated. The conservative management for FAP related intra-abdominal desmoids has also previously been recommended (Clark et al. 1999, Soravia et al. 2000, Nieuwenhuis et al. 2011). Lately, this wait-and-see policy has become more common in desmoid

tumour treatment in general. Many series that describe the successful conservative management of sporadic desmoids have also been published (Bonvalot et al. 2008, Fiore et al. 2009, Bonvalot et al. 2013, Briand et al. 2014, Burtenshaw et al. 2016).

The recurrence rate in our patients was 26%. Among the FAP-related desmoids in our study the recurrence free survival at five years was 50%, but the number of the FAP-related desmoid recurrences was very small to draw definite conclusions. The recurrence free survival in sporadic desmoids was 74% at five years and 72% at 10 and 20 years. Thus, it seems that recurrences occur shortly after the removal of the initial tumour. This has also been noted earlier. The median times for recurrences were reported to be in between 14 and 22 months (Stoeckle et al. 2009, Mullen et al. 2012, Burtenshaw et al. 2016). Other groups have reported recurrence rates that range between 23 and 31% among both FAP-related and sporadic desmoids, and at five years recurrence free survival of 69% among sporadic desmoids (Heiskanen et al. 1996, Stoeckle et al. 2009, Nieuwenhuis et al. 2011, Mullen et al. 2012, Crago et al. 2013, Ihalainen et al. 2015, He et al. 2015). There was a tendency towards lower recurrence rates among R0-resected tumours in our patient population. However, half of the R2-resected patients did not require any other treatment, which may mirror the nature of the course of the desmoid disease. Fourteen per cent of patients with FAP related desmoid, in our series, died because of desmoid tumour related complications. Desmoid tumours in St Marks' hospital resulted in the death of 13% of FAP related desmoid tumour patients (Clark et al. 1999). Desmoid disease together with duodenal cancer is the second most common cause of death among FAP patients (de Campos et al. 2010).

6.4 Limitations of the study

The retrospective studies that are described in this dissertation compared surgical methods and survival. Such a retrospective approach has several inherent limitations regarding the interpretation of the results and the comparison made between the two operation techniques. Moreover, the analysis of the causes that led to secondary proctectomy was subject to bias because many of the operations were performed before the IPAA era, which began in 1992. From the time of starting IRA operations in the 1960s the evolution of overall surgical care pathways has been significant. This is why direct comparison of operations done over several decades may be limited. The data collection from the archival material is also a challenging task. All the information might not have been recorded as meticulously as it is nowadays. In the desmoid studies the data were collected directly from the data files of the Pathology Department of Helsinki. For this reason, only the

biopsy confirmed desmoids were included. There might be patients with only radiographicly confirmed desmoid tumour especially among FAP patients, which are not included in our studies. The accurate histology or the sizes of the tumours and the information about the margins were not always available. Estimating the risk of FAP among initially sporadic desmoid patients in our prospective study was limited by the attendance rate, which was only 61% of all invited patients. Finally, patients with a hereditary syndrome are a specific population of colorectal patients. They usually have many relatives, who died of cancer and they might have their own prejudices and reasons about whether or not to have prophylactic treatment. Indeed, some patients postponed their attendance to screening because of the fear of the cancer and death.

6.5 Future prospects

FAP syndrome has been known about for almost 100 years, the development of all the treatment strategies over that time have changed the prognosis of patients. Colorectal cancer or permanent stomy are not inevitable results anymore. It is interesting to see how survival changes among the more recently diagnosed FAP patients, who have the chance of having current treatment from the beginning. It will also be interesting to see, if the extracolonic manifestations are more common causes of death in the future. Hopefully the treatment of intra-abdominal desmoids will develop in the future.

Our next objective for future studies is to collect more data about the coverage of screening among FAP patients' families. Another objective will be to study their survival and also the reasons why they have dropped-out from the screening programme. The screening for volunteer relatives will be organized. Moreover, extracolonic manifestations other than desmoids are under research.

7. CONCLUSIONS

The main findings of the present series of studies are as follows:

1. IPAA should be the operation of choice for severe and intermediate polyposis, because it carries a better long-term survival without an increased risk of complications. The differences in survival between the two compared procedures are mainly due to the remaining 9% risk of rectal cancer death within the 30-year period after having the IRA operation despite the annual endoscopic follow-up of the rectum. Half of the patients with IRA ended up having a secondary proctectomy during their lifetime. Primary IPAA is also likely to succeed better than secondary IPAA. Only AFAP patients will be the candidates for IRA in the future. In the era of genetic testing, the phenotype should still play a major role in determining the operation technique. However, the family history and genotype should be taken account (I & II).

2. The comparison of survival and mortality between call-ups and probands revealed that the overall survival was better among call-ups. The benefit remained whether the starting date of the survival analysis was the birth date or the date of the proband's diagnosis or the participant's own date of diagnosis (III).

3. The desmoid tumour patients with abdominal symptoms or whose desmoid is located in a truncal region should routinely undergo FAP screening. Screening can be initiated with sigmoidoscopy, but if sigmoidoscopy is negative, the *APC* gene mutation testing should be considered (IV).

4. FAP-related desmoids are more complex in their behaviour than sporadic desmoids. R0 resection should be a goal for treatment. If R0 resection is not possible, then the wait-and-see strategy might be the best alternative. Desmoid tumours are prone to recurrences even among sporadic desmoids, but the risk of death of desmoid tumour is still low among sporadic patients (V).

8. ACKNOWLEDGEMENTS

This study was conducted at the Department of Gastrointestinal surgery, Helsinki University Hospital between 2012 and 2016. I wish to owe my deepest gratitude to all the people who made it possible.

I want to thank Professor Pauli Puolakkainen for the opportunity to carry out this thesis. I thank you for creating an inspiring and supportive academic environment to work. Pauli is also thanked for being a very humane Professor.

I warmly thank Adjunct Professor Anna Lepistö for guiding me throughout the whole thesis process. Anna has my deepest respect for being a great clinician, head of department and researcher. She has also made me believe that you can combine challenging work and family life. Anna has been a great role model by showing that if you work hard and sometimes also outside the office hours you can reach your goals (e.g. she gave comments to my last article on Boxing Day)!

I am also grateful for Professor Heikki Järvinen for all the valuable advice in the beginning of this process and his meticulous record keeping of all the FAP patients during past decades. Heikki is a true father of the FAP research in Finland!

I want to thank the official reviewers of this thesis. Adjunct Professor Ilmo Kellokumpu is thanked for his valuable comments in the fields of surgery and statistics. I also thank Ilmo Kellokumpu, as well as other former colleagues in Jyväskylä, in particular Professor Jukka-Pekka Mecklin (a head of Department of Surgery at that time), from their guidance during my early years as a surgeon. Adjunct Professor Minna Pöyhönen is thanked for her constructive comments, especially in the field of clinical genetics, and for being so understanding for a surgeon who tries to understand genetics. I also thank my brother in-law Professor Juha Koskenvuo, an unofficial reviewer of this thesis for his valuable comments at the very end of this thesis process.

I am thankful for all my co-authors: Professor Päivi Peltomäki, Professor Ari Ristimäki, Harri Mustonen, Janne Pitkäniemi, Matti Rantanen, Annette Gylling and Taina T. Nieminen. My warmest thanks belongs to Laura Renkonen-Sinisalo, who in addition to co-authoring has also been a great mentor in the field of surgery and whose memorable advice since teaching ‘how a surgeon washes hands’ in medical school will not be forgotten. I am

deeply indebted to research secretaries Tuula Lehtinen and Beatriz Alcala-Repo for their help with FAP patients.

I express my warmest thanks to all my colleagues in the Department of Gastrointestinal Surgery, Helsinki University Hospital. I indepted to my superiors Esko Kemppainen, Jukka Sirén and Leena Halme for always being very understanding and supportive in combining clinical work and research. Especially, I thank several colleagues for being always there willing to help and offering a peer-support in research work and personal life, as well as the good company they have been offering during international conferences: Carola Haapamäki, Ilona Keränen, Hanna Lampela, Outi Lindström, Minna Räsänen, Ville Sallinen and Päivi Siironen. My deepest thanks go to Anne Penttilä. It is a privilege to have such a dear friend working in the same field. Also all the co-workers in the ward, nowadays known as M14 are thanked for the warm-hearted working atmosphere you have created there, especially colleagues Monika Carpelan-Holmström and Sini-Marja Sjöblom and nurse manager Maija Eskola-Pellikka are thanked.

I thank all my friends along the way for being always there for me. You make my everyday life more colorful with many joyful moments and help me remember that there is also life outside the hospital. Especial thanks goes to Josu, for the peer-support in every field of life, including this thesis process. All the 'Lääkistytöt' are thanked also for all non-academic nice traditions we have had, such as first of May parties, crayfish parties and pre-Christmas parties.

I owe my deepest thanks to all my in-laws, the big 'Koskenvuo clan' is thanked for the hilarious moments we have had and will have also in future. I am indebted to my mother-in-law Marke, who is always ready to hop on a bus and come to help, and I'm also grateful for your incredibly good immunity when taking care of sick kids.

Above all, I am most grateful to my family for their support during my whole life. I thank my parents Raija and Timo for always being there for me. I have always had a feeling that you are proud of me. You have made me believe 'I can'! And I also thank you for being such a loving grandparents to our sons. And mom should know that without your childcare support our everyday life would sometimes be a disaster. Thank you to my sister Anna for all the memorable moments we have had since childhood. I also thank Mummu and late Taata for teaching me 'Rakastan elämää' mentality and all the family Puustinen is thanked for being always there for me.

Finally my deepest thanks goes to my own family: Ville, Veikko and Voitto. Ville, without your loving and sometimes also disciplined support this thesis would have never happened. You have taught me that everything is possible with hard work, and that hard work does not exclude personal life. I thank Veikko and Voitto for just being adorable themselves. My small boys are also thanked for being so easygoing and good sleepers whenever mom needed to write this 'Värityskirja', a quote from Veikko. I am very fortunate to have my three Vs.

This work was financially supported by research grants from the Helsinki University Hospital, Department of Gastrointestinal surgery Research Funds, The Cancer Society of Finland, The Mary and Georg C. Ehrnrooths foundation and Martti I Turunen foundation, and big part of it was carried out during two maternity leaves supported by good Finnish social security system.

Helsinki 23.8.2016

Laura Koskenvuo

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